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Incorporating National and International Recommendations
(MCI, IAP, NNF, WHO, UNICEF, IPA, ISTP, AAP, etc.)

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Suraj Gupte

12th Edition

Foreword

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The Short Textbook of
Pediatrics

The Short Textbook of **Pediatrics**

Incorporating National and International Recommendations
(MCI, IAP, NNF, WHO, UNICEF, CDC, IPA, ISTP, AAP, etc.)

Twelfth Edition

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Dedicated to

The fond memory of my parents
whose inspiration, motivation, blessings
and moral support continue to contribute a great
deal to my academic endeavors
and
everybody striving to contribute to child health
and welfare for a brighter future
globally.

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Foreword to the Twelfth Edition

I am really at a loss for words to write a *Foreword* for the 12th edition of *The Short Textbook of Pediatrics*, a book which has such a track record and long history of excellence since its first release at the 15th International Congress of Pediatrics in 1977, New Delhi. In fact, a book of this caliber does not need introductions, forewords and endorsements for its continuous success.

The publication of a book is a process as laborious as the process of delivering a baby. Maturity (contents and the quality), weight gain (number of pages) and intact survival (final copy) all have to be carefully looked after. Moreover, bringing out a new edition of a textbook is a tight-rope-walk. There is a need to maintain a continuity in academic contents and advances without affecting the flavor of the earlier editions.

Mercifully, *The Short Textbook of Pediatrics* by Prof Suraj Gupte, an eminent educationist, researcher and author of national and international repute, continues to remain a prestigious publication, highlighting the phenomenal and fast explosion of knowledge in modern pediatrics in edition after edition.

The 12th edition of this book is an excellent combo of clinical pediatrics with recent advances in the field of child health. The value of this textbook is largely due to its expert and authoritative contents by scores of knowledgeable contributors drawn from India and abroad. Every reader should be indebted to the dedicated authors for their hard work, knowledge, thoughtfulness and good judgment in providing a wealth of information in the form of profusely-illustrated and state-of-the-art chapters with spotlight on problems in the Indian subcontinent. In the formative stage of medical career, it is important that a student gets authentic information about different topics.

I am confident that the 12th edition of *The Short Textbook of Pediatrics* will act as a support system for medical teachers and help medical students, especially undergraduates, to "Update Grey cells"! The new edition should be yet more successful in improving the standard of pediatric education and child healthcare in the Indian subcontinent in particular.



Dr Pramod Jog MD, MNAMS, FIAP
President (2016),
Indian Academy of Pediatrics

Preface to the Twelfth Edition

The much-awaited 12th edition of *The Short Textbook of Pediatrics* appears at a time when pediatrics has well established its status as an independent subject in the undergraduate curriculum with a separate examination at university level in India following the laudable endeavors of the *Indian Academy of Pediatrics*.

Since the last edition eminently succeeded in meeting the needs of the undergraduate students, here in the 12th edition we have made further strides to attain the enhanced excellence not only for them but also for the benefit of postgraduates, residents, practitioners and teachers. The goal is to provide a blend of time-honored concepts along with new advances with special emphasis on the needs in the Indian subcontinent.

Each and every chapter stands updated with extensive revisions and/or rewriting, reorganization and additional material. Besides a few new chapters, hundreds of fresh illustrations (clinical photographs, diagrams, algorithms/flow charts), boxes and tables are added. An enlarged Index shall further facilitate easy retrieval of information.

In keeping with the changing needs, two new features have been incorporated at the end of each chapters in the form of self-assessment *Multiple Choice Questions (MCQs)* and *Clinical Problem-solving Reviews*.

As a result, the new edition is yet more reader-friendly, state-of-the-art and practical-oriented. Yet, the hallmarks of the earlier editions, namely brevity with comprehensiveness, simple and straightforward style and easy to understand expression have been retained and, in fact, further strengthened.

Without any shadow of doubt, the unique and enhanced value of the 12th edition is very much on account of the expertise, hard work and command in the respective fields of the distinguished contributors. My hats off to them!

A multitude of colleagues, friends and readers, in India and abroad, made worthy suggestions for enhancing the utility of the book. Informed assistance from the faculty of the Postgraduate Department of Pediatrics, Mamata Medical College and Hospitals, especially Dr G Somaiah, Dr MAM Siddiq and Dr G Arpitha, is particularly acknowledged. Also, the time-to-time academic feedbacks from our residents/postgraduates deserve appreciation.

The Management and the Administration of Mamata Medical College and Hospitals, especially Mr P Nageshwara Rao (Founder), Mr P Ajay Kumar, MLA (Chairman), Dr G Venketeshwara Rao (Medical Director), Dr K Koteswara Rao (Dean), and Dr T Jaysree (Principal) have been gracious enough for blessing the project and for providing moral support and motivation in successfully completing the project.

My wife, Shamma, graciously assisted me so much in taking the project to its logical conclusion. So did my daughter, Dr Novy; son-in-law, Dr Gagan; son, Er Manu; and daughter-in-law, Er Shivani, in spite of their tight schedules and preoccupation. My brothers, Dr Satish, Raji (alas, we lost him some months back!), Subhash and Rajendra's continuing interest in this project and suggestions for the betterment of the book has all along been a support for my endeavors.

Dr Pramod Jog, President (2016), Indian Academy of Pediatrics, has been gracious enough to write a *Foreword* to this edition. My hats off to him for warmly recommending the book.

Finally, I wish to thank Mr Jitendar P Vij (Group Chairman), Mr Ankit Vij (Group President), Ms Chetna Malhotra Vohra (Associate Director-Content Strategy) Jaypee Brothers Medical Publishers (P) Ltd., and their dedicated staff for the skillful production qualities of the 12th edition.

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Preface to the First Edition

"Whyn't a handy pediatric book for our students?"-Requests like this virtually flooded me as I was in the thick of editing the *Newer Horizons in Tropical Pediatrics* last year. Today, I am glad to offer that much-demanded work in the form of *The Short Textbook of Pediatrics*.

The Short Textbook of Pediatrics is aimed at providing a concise, simple and profusely-illustrated digest of the contemporary pediatrics, relevant to the developing world. Common tropical problems, such as nutritional deficiencies, diarrheas, tuberculosis and other frequent infections and parasitic infections and immunization, have received special attention. Certain areas that are important to us but have been ignored by the western authors are, in particular, dealt with. Indian childhood cirrhosis, infantile tremor syndrome, primary bladder stone disease, BCG as a diagnostic tool and tuberculous encephalopathy figure in this list. The accent is on priorities, clinical aspects and latest information rather than on rare conditions and outdated theoretical discussion.

The book is addressed primarily to the medical students, new entrants to the specialty of pediatrics and practising physicians who deal with infants and children as well. Some material especially the statistical data and upto date reference—some as latest as of 1977—are likely to be of value to the seniors either. How far have I succeeded in my endeavors? In this behalf, I would love to have your assessment. That shall help me to make up the deficiencies and introduce the "necessary changes for the better" in the future edition.

The publisher, Mr Jitendar P Vij of M/s Jaypee Brothers Medical Publishers (P) Ltd., and the Managing Editor, Rajendra Gupte's contributions have been vital to the appearance of this manual.

Much of the material included in *The Short Textbook of Pediatrics* is based on articles in the recent WHO/UNICEF publications, *Indian Journal of Pediatrics*, *Indian Pediatrics*, *Indian Practitioner* and other Indian and foreign periodicals and books. I have punctuated the accounts with our own observations at the prestigious Postgraduate Institute of Medical Education and Research, Chandigarh, HP Medical College, Shimla, and Govt. Medical College, Jammu. The superb teaching of Prof BNS Walia, Dr (Mrs) Saroj Mehta, Dr ON Bhakoo, Dr SK Mehta, Dr (Mrs) A Perakash and Col ML Magotra has proved to be a source of guidance and stimulation in preparing this book.

Hats off to many of my past and present colleagues, friends and well-wishers for lots of good-will, ideas and cooperation; Dr JC Lall, Dr RK Chaudhary, Dr (Miss) Kalpana Kohli, Dr (Miss) Rita Malhotra, Dr Vinod Seth, Mrs Neelam Virmani, Mr Ayudhia Kaul and Mr GS Malhotra deserve a special mention. Dr Satish Gupte, Dr (Miss) Prem Gupte and Miss Shamma Bakshi extended enthusiastic assistance in preparing the manuscript, proof-reading and indexing.

Major (Mrs) BK Sohi and Lt. Col AS Sohi have been exceedingly courteous in making available a number of excellent clinical photographs. I must also acknowledge the help received from Prof H Shirkey, Dr Roy Brown, Prof Ashfaq Ahmad and Dr VK Dogra.

Prof NS Tibrewala has been kind enough to write the *Foreword* in spite of his preoccupations, especially as President of the forthcoming *15th International Congress of Pediatrics*. He has indeed done me an honor.

Principal NS Pathania, Prof SS Manchanda, Prof PM Udani, Prof RS Dayal and Prof VB Raju figure among our eminent medical men who graciously blessed this project. I should record my appreciation of the fond interest evinced in this manual by Mr KA Padmanabhan, Mr Suraj Saraf and Dr K Chaudhry—all leading journalists.

Finally, I greatly value the favors extended by my folks through various stages of this publication. My kid sister, Veenu and brothers, Subhash and Raji helped me in many a way. They would cheer me up as and when I found the going tough.

To all of them, plus all those who contributed but are not identified here, I am highly grateful.

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- *Recent Advances in Pediatrics* by Suraj Gupte, *Differential Diagnosis in Pediatrics* by Suraj Gupte, *Annales Nestle*, *The Short Textbook of Medical Microbiology* by Satish Gupte, UNICEF, CDC, and Dr Anupam Gandhi (Johannesburg), Dr Mohd Afzal (Karachi), Dr Surya N Thapa (Kathmandu) and Dr G Arpitha (Khammam) for some illustrative figures carried in this book.
- Medical journals, identified under "Excerpts from Journals" (see cover [back]), for critical reviews
- Various medical periodicals, journals, chronicles, bulletins, proceedings of conferences, websites and books for citing their references in the state-of-the-art chapters for "Further Reading".

Every attempt has been made to acknowledge the sources of information at concerned points, in further reading and/or here. Omission, if any, is unintentional and is regretted.

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SECTION 1

Introduction to Pediatrics

Section Outline

- I. Pediatrics: Contemporary Trends

DEFINITION AND ORIGIN

By modern definition, ***pediatrics is the study of the child from the very conception through infancy, childhood and adolescence to adulthood.***

In other words, pediatrics is the medical science (the science of right living), which enables an anticipated newborn to grow into a healthy adult, useful to the society.

The term, pediatrics, is derived from the Greek words ***pedia*** (meaning a child or pertaining to a child), ***iatrike*** (meaning treatment) and ***ics*** (meaning a branch of science). As already pointed out, the contemporary understanding of this Greek term is—***science of child care, preventive as well as curative.***

Pediatrics, therefore, is concerned with the health of infants, children and adolescents, their growth and development, and attaining full potential as adults. A pediatrician's responsibility is not only to care for the physical, mental and emotional health from conception to maturity, but also to demonstrate concern for the social, environmental and cultural influences that are known to have considerable fallout on children and their families.

Among the factors that have a bearing on health problems of children rank climate, environment and geography, prevalence and ecology of infectious agents and their hosts, agricultural resources and practices, education, economic, social and cultural considerations, stage of urbanization and industrialization, and gene frequencies.

In United States of America, pediatrics includes individuals upto the age of 21 years. United Nations Children's Emergency Fund (UNICEF) is content with ***upto 18 years*** as the pediatric age group. According to the Indian Academy of Pediatrics (IAP), health problems of children upto 18 years (inclusive) should be the responsibility of pediatricians.

PEDIATRICS AS AN INDEPENDENT AND UNIQUE SPECIALTY

There are quite a few logics for regarding pediatrics as an independent medical specialty.

- **First**, the health problems of children differ from those of adults in many a way.
- **Secondly**, children's response to an illness is influenced by age.
- **Thirdly**, management of childhood illness is significantly at variance with that of an adult.

- **Finally**, children also need special care since they are world's most important resource and amongst the most vulnerable in the society.

This modern concept of pediatrics lends it a unique status. Unlike other specialities, it deals with the excitingly dynamic process of continuous care of the growing child, ***not the whole child.*** The semantic whole child, according to UNICEF, means that assistance for meeting the needs of children should no longer be restricted only to nutrition which is of immediate benefit to them. Instead, it should be broad based and geared to their long-term personal development and to the development of the countries in which they live. This approach is called ***country health programming.*** The differences between a child and an adult are appropriately spelt in the saying, ***the child is not a little man or the child is not a miniature adult.***

CHANGING PEDIATRIC SCENARIO

Pediatrics as a discipline per se took birth in 19th century in the prosperous countries of the West. Notwithstanding the fact that health care of children occupied pride of place in the ancient Indian health system (also in Chinese and Greek systems), formal recognition of pediatrics as a discipline is too much young in India and other resource limited countries. Paradoxically, over one-half of the world's total children (1.5 billion out of 3 billion) live in these regions. In India, for instance, around 40% of the 1.25 billion population is constituted by the most vulnerable segment, i.e. infants and children. Further, a high proportion of the total morbidity and mortality is accounted by the pediatric age group. The corresponding figures for the prosperous countries are considerably low.

Apparently, appreciation of the significance of child care has come rather late. Let us hope it is not too late! In India, for example, our achievements in child health and care are a cocktail of ***success, lukewarm success and failure.***

On the positive front, we can take pride in:

- Total eradication of smallpox,
- Total eradication of guineaworm,
- Success of oral rehydration therapy,
- Maternal and neonatal tetanus-free status,
- Polio free status,
- Fall in incidence of serious forms of tuberculosis,
- Fall in mortality from tuberculosis,
- Fall in prevalence of severe malnutrition,
- Fall in mortality from diarrheal disease,

Table 1.1: Important current indices of child mortality in India in 2014–2015

Mortality index	Mortality/1000 live births
PMR/ENMR	20
NMR	24
IMR	36
U-5MR	50

Abbreviations: PMR, perinatal mortality index; ENMR, early neonatal mortality rate; NMR, neonatal mortality rate; IMR, infant mortality rate; U-5MR, under-5 mortality rate.

- Five-fold hike in school enrolment of girls since independence,
- Fall in infant, perinatal, neonatal and under 5 mortality rates.

On the negative (somewhat failure) front, we have:

- Persistence of still high incidence of tuberculosis and emergence of resistant strains,
- Still high child mortality indices (Table 1.1),
- Inadequate availability of safe drinking water,
- Insufficient sewage disposal,
- Still unacceptably high dropout rate in schools (especially in case of girls).

In other words, pediatrics which was by and large a scratch in India (just a poor appendage of general/internal medicine) when it became independent in 1947, has come a long way. Yet, the progress has fallen short of what should have been attained.

A large chunk of pediatricians (90%) in the Indian sub-continent (perhaps in most developing countries) are generalist though many of them have an area or two of special interest. Thus, by and large, each and every pediatrician is seemingly doing everything. In institutions, growth of subspecialties such as neonatology, cardiology, nephrology, gastroenterology, hematology, neurology, endocrinology, allergy, pulmonology, etc. is beginning to be palpable.

Despite the fact that some centers have started these subspecialties, their growth remains quite slow, except for, perhaps, neonatology. More recently, voice has been raised to develop pediatric subspecialty divisions in all medical colleges. It has been argued that denial of a super/sub-specialty care to children has no justification whatsoever.

At the same time, it is felt that a spirit of partnership and shared responsibility should be developed between the limited number of pediatric subspecialists and the general pediatricians and the physicians who still continue to offer pediatric care as well. In this context, the initiative of the IAP to ask its subspecialty chapters to prepare guidelines for management of common pediatric problems, which can be put on Internet and linked to the IAP website, is indeed commendable. There is a need for affiliation of the IAP subspecialty chapters with the subspecialty international associations. Hopefully, this development would contribute to the development of the subspecialties at an international level.

Adolescent medicine, though fairly well-established in the West, is yet at a conceptual stage in India and neighboring countries. The IAP has advocated that pediatric care be

Box 1.1 Mission Kishore Uday: Major approaches

- Intervention by counseling on normal body development
- Avoiding or minimizing the risk-taking behavior
- Sexuality issues
- Positive parenting
- Effective communication



Fig. 1.1: Adolescent Health. This no-man's land, neglected by physicians as well as pediatricians, is now beginning to receive increasing attention from pediatricians. IAP's *Mission Kishore Uday* is a worthy step in this behalf.

extended upto (and including) 18 years age. As a matter of fact, a commendable beginning was made in India with the declaration of the year 2000 as the IAP (*year for the adolescence and child at risk*). Subsequently, every year we continue to observe IAP (*child and adolescent health care week*) in the month of November, ensuring that 14 November essentially falls within the week.

More recently, IAP has launched a fresh initiative—**Mission Kishore Uday**, which aimed at addressing the health needs of the adolescents in India (Box 1.1). Hopefully, the mission shall contribute to better health and wellness for our teenagers (Fig. 1.1).

Apart from the practicing pediatricians, the collaboration from the international agencies like World Health Organization (WHO) and UNICEF and Non-Governmental Organizations (NGOs) like Child Rights and You (CRY), in addition to the Union and State Governments, is a must for success of the strategy. Also, See Chapter 7 (Adolescent Medicine).

CHILD HEALTH IN INDIA'S NATIONAL HEALTH SYSTEM

National programs on child health include universal immunization program (UIP), diarrheal disease control program, respiratory infections control program, child survival and safe motherhood program (CSSM), reproductive and child health (RCH) program, etc.

NATIONAL HEALTH MISSION

It was launched in 2005. This is India's umbrella program under which many schemes, initiatives and programs have

been brought to provide universal access to quality health care. Its major subunits are—National Rural Health Mission (NRHM) and National Urban Health Mission (NUHM).

National Rural Health Mission

India's flagship health initiative, the NRHM is an initiative undertaken by the Government of India (GoI) to address the health needs of underserved rural areas. Its major goal is providing accessible, affordable, accountable, effective and reliable primary health care, and bridging the gap in rural health care through creation of cadre of Accredited Social Health Activists (ASHA). This mission integrates multiple vertical programs.

It was launched in 2005; NRHM was initially tasked with addressing the health needs of 18 states that had been identified as having weak public health indicators. Under the NRHM, the empowered action group (EAG) States as well as North Eastern States, Jammu and Kashmir and Himachal Pradesh have been given special thrust.

The spotlight is on establishing a fully functional, community owned, decentralized health delivery system with intersectoral convergence at all levels, to ensure simultaneous action on a wide range of determinants of health such as water, sanitation, education, nutrition, social and gender equality. Institutional integration within the fragmented health sector was expected to provide a focus on outcomes, measured against Indian public health standards for all health facilities.

The focus on covering rural areas and rural population will continue along with upscaling of NRHM to include non-communicable diseases and expanding health coverage to urban areas.

Reproductive, Maternal, Newborn, Child and Adolescent Health (RMNCH + A) Strategy

Realizing need for extra thrust on neonatal and adolescent health, a new program, Reproductive, Maternal, Newborn, Child and Adolescent Health (RMNCH + A) strategy was launched in 2013 under the NRHM.

The RMNCH + A strategy is based on provision of comprehensive care through five pillars, or thematic areas of reproductive, maternal, neonatal, child, and adolescent health, and is guided by central tenets of equity, universal care, entitlement, and accountability. The plus within the strategy focuses on:

- Including adolescence for the first time as a distinct life stage,
- Linking maternal and child health to reproductive health, family planning, adolescent health, human immunodeficiency virus (HIV), gender, and pre-conception and prenatal diagnostic techniques,
- Linking home and community based services to facility based care,
- Ensuring linkages, referrals, and counter referrals between and among health facilities.

Rural health with emphasis on child health, in particular occupies a central place in India's health policy as depicted in pyramid with subcenters at the bottom through com-

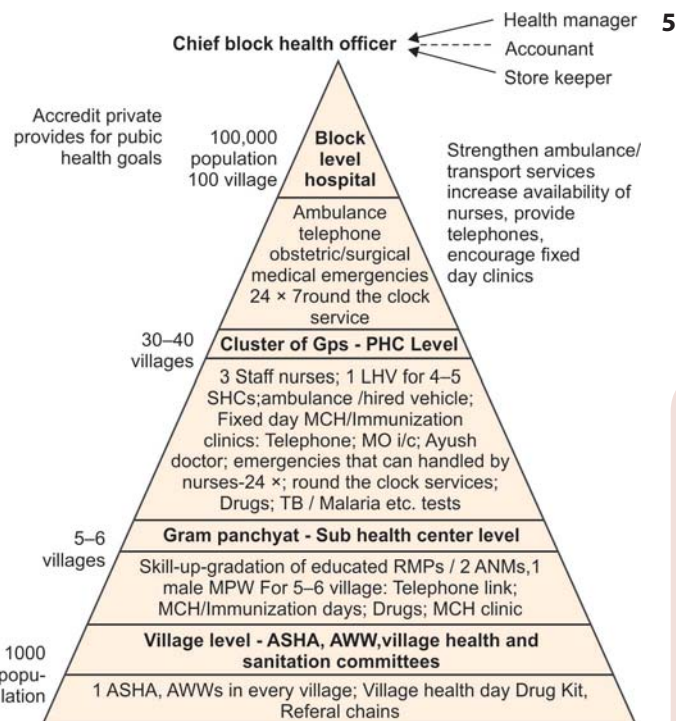


Fig. 1.2: A pyramid representation of NRHM structure. Note that at the base are subcenters which are fed by the frontline workers: Accredited Social Health Activist (ASHA), and Anganwadi Workers (AWW). On top is the Block-level hospital.

munity health centers in the middle and medical college(s)/ tertiary hospitals on top (Fig. 1.2).

National Urban Health Mission

National Urban Health Mission aims at improving the health status of the urban poor, especially slum dwellers, thrust on public health—sanitation, clean drinking water, vector control, etc. and strengthening public health capacity of urban local bodies.

INDIA NEWBORN ACTION PLAN

India newborn action plan (INAP) in operation since 2014 outlines a targeted strategy for accelerating the reduction preventable newborn deaths and stillbirths. It defines the latest evidence on effective interventions which are likely to contribute to reduction in the burden of stillbirths, perinatal and neonatal mortality and maternal deaths. The goal is to achieve a single digit stillbirth and neonatal mortality rate by 2030.

CHILD HEALTH IN INDIA'S 12TH FIVE YEAR PLAN

The 12th five year plan (2012–2017), aimed at working towards national health outcome goals, carries two significant target health indicators:

1. Reduction in infant mortality rate (IMR) to 25. Now that the IMR is 36, an achievement of 25 by 2017 is workable only if the current rate of decline (5–6% every year) gets accelerated.
2. Prevention and reduction in undernutrition in children under 3 years to half of levels of national family health

- 6 survey (NFHS-3) (conducted in 2005–6). At present rate of decline, the estimated prevalence of underweight children in India is 29%. To achieve the 12th five year plan goal by 2017, India needs to accelerate the decline rate. The Millennium Development Goal (MDG) by 2015 is 26%. In 2015, we are little short of meeting even that.

Since child and mother is supposed to be a single unit, it would not be out of place to make a passing reference to projections in the plan concerning the maternal mortality rate, reduction in maternal mortality rate (MMR) to 100 by 2017 is the goal of the plan. The estimated MMR in 2015 is 139. At the present 5.8% yearly decline, India can achieve only a MMR of around 123 by 2017. In order to meet the projected target of 100, an accelerated decline in rate is needed.

INDIA'S NEW NATIONAL HEALTH POLICY

Mercifully, the GoI has now drafted 2015 National health policy which promises a hike of 2.5% of GDP on health care. The impact of this hike on child health and survival are likely to be considerable.

TROPICAL PEDIATRICS: RADICAL CONCEPT

Literally, the term, **tropical pediatrics**, denotes care of children in the tropical countries, i.e. countries occupying the region between tropic of Cancer and tropic of Capricorn. With the exception of Australia and Singapore, all these countries are disadvantaged on account of economical deprivation. In majority of these countries, the per capita income is under US \$775. High infant mortality and under-5 mortality rates are common denominators; so are the **parasitic diseases**. Despite tropical environmental factors, Malaysia and Sri Lanka are successfully catching up with an IMR of 10 and under-5 mortality rate of 11/1000 livebirths.

The so-called **tropical diseases** are no longer restricted to the tropics only. Factors such as globalization and shrinkage of the world with a free exchange of vectors and microorganisms have spread them to the non-tropical countries such as those of Europe and America with special involvement of the underprivileged. Afghanistan is a glaring example of a country outside the tropics hit by the tropical diseases as a result of two decades of civil war. Its infant mortality is as high as 175/1000 livebirths.

Thus, more crucial than the tropical environment in development of tropical diseases is the economy and living standard of the community. For this reason, we need to redefine the term, tropical pediatrics, as **care of children of the economically disadvantaged communities, not only in the tropical countries, but also in the non-tropical countries**.

RIGHTS OF THE CHILD: YESTERDAY, TODAY AND TOMORROW

CHILD RIGHTS UNDER UNITED NATIONS

- The **United Nations' declaration of the rights of the child** as far back as in 1959 (Box 1.2), to which India

Box 1.2

Ten basic rights of children as per United Nations' Declaration of 1959

1. The child shall be brought up in a spirit of understanding, friendship, peace and universal brotherhood and shall not be exposed to racial, religious or other forms of discrimination.
2. The child shall be protected against all forms of neglect, cruelty, exploitation and traffic and shall not be permitted to be employed before an appropriate minimum age.
3. The child shall, in all circumstances, be among the first to receive protection and relief.
4. The child entitled to free and compulsory elementary education and such an education as is in his best interests for which the parents are to be responsible.
5. The child is entitled to grow up in an atmosphere of affection and moral and material security, with public authorities taking care of children without families or other support.
6. The physically, mentally or socially handicapped child shall be entitled for special treatment, education and appropriate care.
7. The child shall have the right to adequate nutrition, housing, recreation and medical services, including special health care and protection and postnatal care for the mother.
8. The child shall be entitled to a name and a nationality.
9. The child shall enjoy special protection to be able to develop in every way in conditions of freedom and dignity.
10. All children—irrespective of their race, color, sex or creed of their parents shall be entitled to these rights.

is a signatory, gives the child pride of place, as also makes the people aware of his needs and rights and their duties towards him.

- **Defense for Children International**, Geneva, has been in operation since 1979 to ensure ongoing, systemic international action, especially directed towards promoting and protecting the rights of the child. November 14 is observed as **Universal Children's Day** ever since 1954. The United Nations has assigned the responsibility to promote this annual day to the UNICEF. Since 1989 the realization that children have special needs and hence the special rights have given birth to an international law in the shape of **Convention on the Rights of the Child** (CRC). The provision of the Convention was confirmed in 1990 by the **World Summit for Children**. Now, the Convention is credited as the most widely ratified human rights treaty in the world.

Empowered with 54 Articles, the Convention defines children as people below the age 18 years (Article 1) whose best interests must be taken into account in all situations (Article 3). It protects children's right to survive and develop (Article 6) to their full potential, and among its provisions are those affirming children's right to the highest attainable standard of health care (Article 24) as shown in Figure 1.3 and to express views (Article 12) and receive information (Article 13). According to article 28, the states are obliged to make primary education compulsory and available to all children. Children have a right to be registered immediately after birth and to have name and nationality (Article 31) and to protection from all forms of exploitation and sexual abuse (Article 34).

Among the large number of countries that have adopted comprehensive child rights legislation in their children's act following the birth of the Convention rank as small a country as Nepal.



Fig. 1.3: Child Rights Protection. Convention on rights of the Child (1989–90) promises protection of children's right to survive and develop to their full potential, and affirms children's right to the highest attainable standard of health care.



Fig. 1.4: Elementary Education. Every child's right. Compulsory and free elementary education is one of the 10 fundamental rights of the child to which India too is committed.



Fig. 1.5: Child's Right to Education and the Government. Provision of facilities for free elementary education is the responsibility of the government. However, the onus lies on the parents to ensure that child obtains such an education rather than have him involved in activities that amount to school withdrawal.



Fig. 1.6: Child's Right to Education and Parents. As high as 130 million (21%) primary school age children in the resource-limited world do not attend school out of a total of 625 million children of this age group in these countries thanks to reasons on parental side.

Mercifully, notable advances have been made during the last decade of the 20th century and the subsequent years of the present century for the welfare of children, including:

- Laws to safeguard them from suffering and exploitation,
- Near eradication of poliomyelitis,
- Reduction of morbidity and mortality from neonatal tetanus and measles,
- Fall in vitamin A deficiency (VAD) blindness,
- Reduction in deaths from diarrheal dehydration,
- Sensitization of people against child labor and CAN, etc.

Today, more children are born healthy and more are immunized, more can read and write, and more are free to learn, play and simply live as children than would have been thought possible years ago, according to a UNICEF report. This is the direct result of translation of the commitments made in the Convention into concrete action.

Yet, for all the gains made, violations of children's rights, particularly in the resource limited world, continue to be breathtaking, ranging from failure to register births and provide healthcare and education (Figs 1.4 and 1.5) to exploitation in the form of child labor, abuse and neglect (Fig. 1.6), and involvement of adolescents in terrorist and militancy-related armed conflicts. As aptly put by the UNICEF:

- Every day that nations fail to meet their moral and legal obligations to realize the rights of children, 30,500 boys and girls under-5 years die of primarily preventable diseases.
- Every month that the full-scale campaign needed to stop the HIV/AIDS pandemics is postponed, 250,000 children and young people become infected with the fatal virus.
- Every year that Governments fail to spend for the basic social services or slash developmental assistance, millions of children across the developing world stand deprived of access to safe drinking water and sanitation facilities as also health and school services that are vital for their survival and growth and development.

Undoubtedly, there is a strong case for a social movement to fan the flame that burned years ago for rights of the child and the adolescent for smooth navigation into adulthood. This is particularly a must for advancing human development in the developing countries and those of us responsible for health and care of children and adolescents must in particular take it as a call for vision and leadership to realize a new dream of humankind, free from poverty, disease and discrimination.

- 8 It is pertinent to recall the historic general assembly special session on children, held in 2002 to which, for the first time a large number of children were included as official members of the delegations. True to the spirit of the convention on the rights of the child, the assembly gave a call for considering the views of children and young people when decisions that affect their lives are being made.

CHILD RIGHTS IN INDIA

In India's Constitution, Article 24 prohibits employment of children below the age of 14 years in factories. Article 24 prevents abuse of children of tender age. In Article 45 is incorporated provision of free and compulsory education for all children until they complete the age of 14 years (Figs 1.4 and 1.5).

Thus, India's Constitution undertakes to guarantee equality before the law, pledging special protection for children.

Subsequent to India's accepting the obligations of united nations convention on the rights of the child, following are some of the initiatives launched by India towards advancement, promotion and protection of child rights:

- National commission for protection of child rights.
- National plan of action for children.
- Right to education.

CHILD RIGHTS ADVOCACY AND THE PEDIATRICIANS

More often than not, children are vulnerable and disadvantaged in the society. Undoubtedly, they are in need of a special attention. A global perspective for the field of pediatrics is, therefore, not just desirable, but mandatory.

Since children are usually not in a position to speak out and advocate for themselves, it is the pediatricians who need to advocate for them in order to advance children's well-being and welfare. This applies to all children across the board, regardless of national boundaries, ethnicity, race, religion, culture, and gender. Pediatricians need to create awareness:

- For child's nutrition, growth and development, education and, in fact, overall care so that the child not only survives, but also grows into a healthy adult useful to himself, the family and the society.
- Against exploitation, neglect and abuse, child labor (Figs 1.6 and 1.7), trafficking, etc.

Furthermore, pediatricians need to provide a platform or contribute to it for promotion of coordinated child-centric endeavors with involvement of like minded groups of social workers, teachers, psychologists, child rights activists and community leaders. Collaboration with national and international NGOs is useful to positively influence the government to model its policy in keeping with the UN convention on child rights. The scenario in India is no better.

CONTEMPORARY DISEASE PATTERN AND CHANGING CONCERNS

Disease pattern amongst under-5s in India (Fig. 1.8) is at considerable variance with that of developed world (Fig 1.9). Every year, 70% of deaths in children are due



Fig. 1.7: Child Labor. Gateway to deprivation of child rights to education. Child labor, often encouraged by parents for one or the other reason, is the most important cause of school withdrawal and dropout.

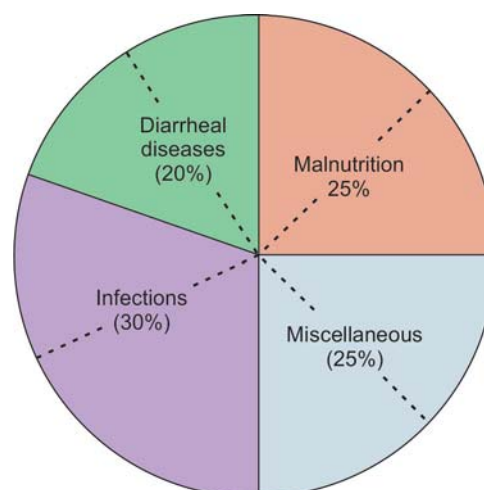


Fig. 1.8: Childhood Disease Pattern in Resource-limited World. Relative frequency of diseases responsible for admission of infants and children in Indian hospitals show predominance of malnutrition, diarrheal diseases and infectious diseases. Dotted lines indicate much overlap.

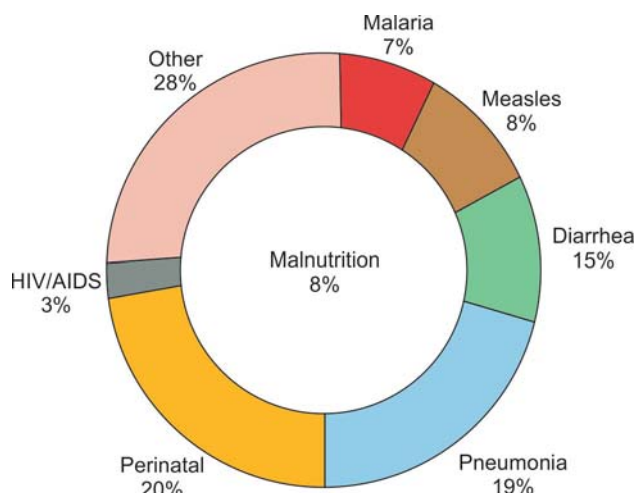


Fig. 1.9: Childhood Disease Pattern in Developed World. Distribution of disease pattern in developed world in the under-5 populations shows predominance of perinatal problems and pneumonias and other infections.

to respiratory infections, diarrheas, measles, malaria or malnutrition. Figure 1.9 gives a rough idea about the disease pattern in patients admitted to our pediatric indoors. With some variations, which are bound to be there from region to region, observations from various parts of India indicate a remarkably similar pattern. This is true of some of our neighboring countries like Bangladesh, Bhutan, Myanmar, Pakistan, Afghanistan, Sri Lanka, Indonesia and Nepal as well.

An appraisal of the health statistics makes it clear that the scene is dominated by malnutrition (primarily the so-called **protein-energy malnutrition**), serious systemic infections (primarily tuberculosis, pneumonias, malaria, measles) and diarrheal disease. These have a considerable overlap on each other and, in broad sense, account for 75% of the cases. The remaining of the so many diseases is responsible for a mere 25% of the admissions.

NUTRITIONAL DEFICIENCY STATES

Nutritional deficiency states constitute a major public health problem in India and other resource limited counties.

Though incidence of severe malnutrition, especially acute severe malnutrition (ASM) in the form of kwashiorkor and marasmus has considerably fallen, mild to moderate malnutrition (Figs 1.10A and B) continues to be a cause of concern. According to the National Family Health Survey-3, nearly one-half of the under-5s are stunted (Fig. 1.11) whereas around 43% are underweight, the major brunt being borne by the rural children. Over and above this, there is high incidence of micronutrient deficiencies (the so-called **hidden hunger**), particularly in relation to iron, vitamin A, iodine, zinc, etc.

Paradoxically, whereas endeavors are focused on controlling under nutrition, children from affluent families are beginning to suffer from overweight and obesity in a big way (Fig. 1.12). The current prevalence of childhood overweight in India is estimated to be 4–22%. Studies from India and other countries have demonstrated an association between overweight and psychosocial risk factors such as a depression, anxiety and social withdrawal.



Figs 1.10A and B: Malnutrition A Challenge. Notwithstanding considerable decline in incidence of severe malnutrition, mild-to-moderate malnutrition is rampant in Indian children, especially in the rural and peri urban settings.



Fig. 1.11: Stunting. A Major Handicap. India has the highest number of stunted children below the age of 5 in the world. According to UNICEF, 62 million children aged less than 5 years suffer from nutritional stunting that contributes to reduced physical and cognitive development.

Courtesy: UNICEF.



Fig. 1.12: Childhood Obesity. A Challenge. Of late, obesity in children and adolescents too is emerging as a big challenge in India and other resource-poor countries. It is central to such comorbidities as hypertension, type 2 diabetes, cardiovascular disease, hyperlipidosis and metabolic syndrome.

India, therefore, appears to be in the thick of what may be termed—**dual nutrition burden**. This implies that India is not only struggling with childhood malnutrition, but is also a fast weight gaining nation, heading for enhanced epidemic of lifestyle diseases not only in adults, but also in children and adolescents.

Infectious Diseases

Infections are another major cause of pediatric morbidity. With considerable reduction in prevalence of preventable childhood infectious diseases, the dominance is now taken over by respiratory and gastrointestinal infections.

- Acute respiratory infections (ARIs) are responsible for 20 to 60% of outpatient attendance, 12 to 45% of admissions and 33% of mortality in the developing world, directly or indirectly. Over 15 to 20% of preschool mortality is related to ARIs, especially pneumonias.
- Though polio and neonatal tetanus stand eliminated, measles continues to cause considerable morbidity and mortality in India and other World Health Organization (WHO) SEAR countries.

- 10 ■ WHO is committed to eliminate measles in whole SEAR by 2020. To achieve the goal in India, GoI has introduced 2-dose strategy for measles vaccine in routine immunization. According to IAP, it is advisable to give measles vaccine as a component of measles, mumps and rubella (MMR), even when it comes to first (9 month) dose rather than alone to provide extended benefit.
- Childhood's tuberculosis and malaria and other mosquito-borne infectious diseases continue to be rampant.
 - Emerging and re-emerging infectious diseases too are a threat.

Diarrheal Diseases

Diarrheal diseases constitute yet another leading cause of morbidity and mortality. Almost 500 million children suffer from acute diarrhea annually. Of them, 5 million die every year. In India alone, nearly 1.5 million children become a casualty due to acute diarrhea every year. Widespread use of oral rehydration therapy (ORS) has led to decline in morbidity and mortality. However, incidence of diarrheal disease continues to be high in the underprivileged section.

The Camel-back Concept

As is obvious, the book picture of a disease is less likely to be seen in our practice and circumstances. A 6-year-old, presenting with acute dysentery, may have significant malnutrition also. To cap this, he may have pulmonary tuberculosis. That is not the end, however. Such a child, as we have often seen, may have one or more intestinal parasitic infestations and skin infections like scabies and pyoderma.

Thus, one finds a multiplicity of ailments in a single child. This kind of a patient has been compared to a **camel-back**.

This observation has been made by us and by others in this country and also in other developing countries where people continue to be underprivileged. This consideration, in particular has contributed to the launching of **Integrated Management of Childhood Illness** (IMCI) scheme by the WHO and UNICEF. The program has already assumed the status of a dominant child health and welfare program in India. A brief deliberation on the strategy is presented in Chapter 9 (Community Pediatrics).

Emerging Issues

Mercifully, there is a greater appreciation of the emergence of such newly recognized problems as HIV/AIDS, drug abuse among teenagers, child abuse and neglect (CAN), street children, child labor, discrimination against girl child, etc. and need to meet their challenge.

HIV/AIDS alone appears to be threatening to nullify all benefits from national health programs aimed at welfare of children.

UNFOUNDED BELIEFS: A ROADBLOCK

What is particularly disappointing in relation to the developing world is that even as we are in the second

decade of the 21st century, illiteracy, ignorance, superstitions, cultural and religious practices and rituals continue to have considerable influence in the area of health and nutrition.

Howsoever, incredible it may seem, many folks still think diseases are the "outcome of the curse". Quite a proportion of them rely on witchcraft for their treatment. In a pilot study, we found that 40% of the slum parents believed that the **disease can be caused by the wrath of deities (supernatural beings), a posthumous world of dead ancestors and magical concepts**.

QUALITY OF LIFE

Despite improvement in the vital pediatric statistics, quality of life is generally not upto the mark. Almost 1/3rd of the pediatric population has a deplorable existence. About one-half of our pediatric population can be classified as unhealthy and surviving with impaired bodies and, perhaps, intellects. Various interrelated conditions such as malnutrition, diarrheal disease, infections like tuberculosis, acute respiratory infection (ARI), parasitic infestations, etc. contribute to ill health and poor growth. Over 50% of children are undernourished. The most vulnerable period for malnutrition is first 3 years (usually 6 months to 2 years) of life. The consequences of too many mouths-to-feed and the lack of fool-proof system of health care with an accent on the rural and the urban poor and other social services against a backdrop of generally poor socioeconomic status further aggravate the situation.

In a nutshell, admittedly, climatic, geographical and ethnic factors play some role for the remarkable difference in disease pattern between Indian subcontinent and rest of the developing world and developed world. However, of much greater significance are factors like socioeconomic conditions, hygiene and sanitation, culture, education and local medical and health facilities. Indeed, these need consideration and thrust of the policy-makers and think-tanks.

MORTALITY SCENARIO AND DELIVERY OF CHILD HEALTH CARE

Box 1.3, Table 1.2 and Figures 1.13 and 1.14 give a broad idea of the under-5 mortality scenario in the developing world.

Today, a child in India has far better chances of survival with the life expectancy of around 68 (males 67.3, females 69.6) than 3 or 4 decades back. However, the situation is still far from satisfactory.

- The **current IMR** of 36 per 1,000 live-births (from 129 in 1970) is still many times higher than in the advanced

Box 1.3 Broad mortality data in India

- 50% of all deaths occur below 5 years
- 33% of all deaths occur below 1 year
- 20% of all deaths occur below 1 month
- 10% of all deaths occur below 1 week

Table 1.2: Some current indices of child and maternal mortality in India and other countries

Mortality index	PMR	NMR	IMR	U-5MR	MMR
India	20	24	36	50	190
Pakistan	40	42	69	86	170
Sri Lanka	–	6	8	10	29
Bangladesh	28	24	33	41	170
Afghanistan	28	36	70	99	400
Japan	Negligible	1	2	3	6
Sweden	Negligible	2	2	3	4
United states	Negligible	4	6	7	28

Abbreviations: PMR, perinatal mortality rate; NMR, neonatal mortality rate; IMR, infant mortality rate; U-5MR, under-5 mortality rate; MMR, maternal mortality rate.

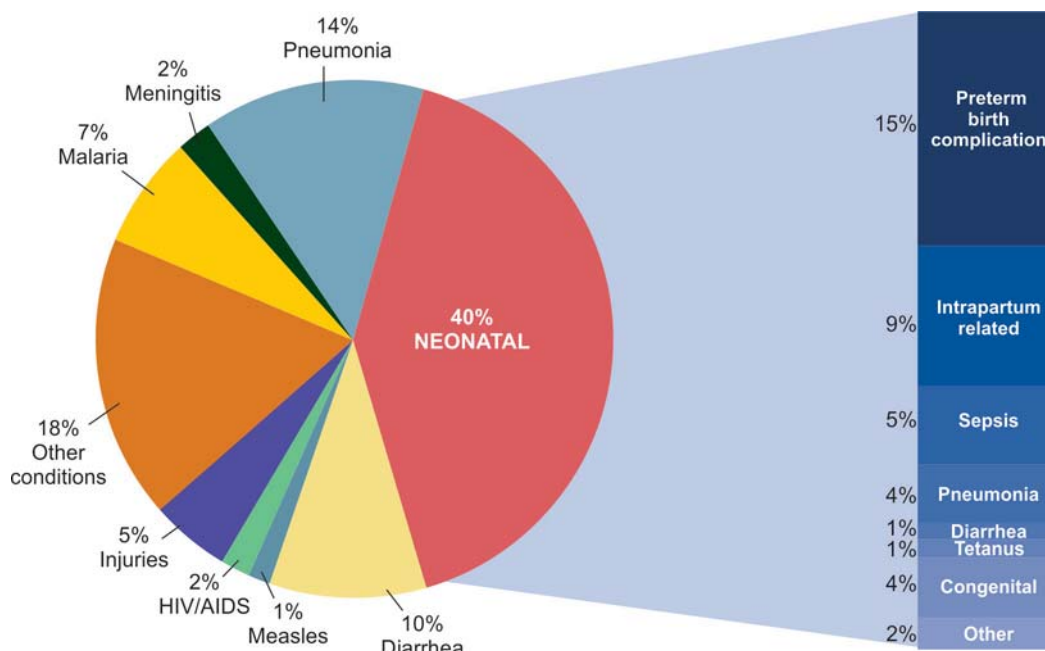


Fig. 1.13: Under 5-mortality Scenario. Note that around 40% of total mortality is constituted by the neonatal deaths followed by lower respiratory tract infections (pneumonias), diarrhea and malaria.

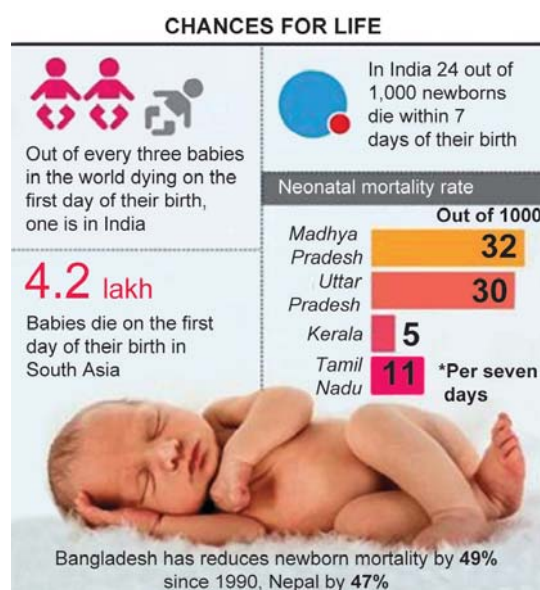


Fig. 1.14: Neonatal deaths. In India, neonates contribute to 40% under-5 mortality rate.

Source: The Hindu, Chennai, India.

countries (Table 1.2). Vast state-wise variations are noteworthy with Kerala having IMR of 13 and Orissa 93. Likewise, urban India has much lower IMR compared to rural India. UNICEF has estimated an IMR of 35 by 2020 in India. GoI is committed to achieve an IMR of 27 by 20–17. IAP has proposed a yet more ambitious target, Mission 20:20 (IMR 20 at 2020).

- **Perinatal mortality** (a reliable index of status of women and their health and the quality of antenatal, natal and neonatal care) of 20/1000 livebirths in India is far higher than 10 to 15 in most developed countries. It is estimated that 3 perinates die in India every minute amounting to a huge human wastage of 1.5 million perinates every year. Likewise neonatal mortality rate (NMR) is 24/1000 live births compared to a figure of 1–4/1000 live births in prosperous countries. About 60% of the infant mortality is accounted by neonatal deaths. GoI is committed to achieve a single digit neonatal mortality rate (NMR) by 2030.

Factors responsible for continued high (though reduced) perinatal/neonatal mortality include:

- 12 ■ Vicious cycles of frequent pregnancies,
 ■ Compromised maternal health and nutrition,
 ■ High incidence of low birth weight, and, in consequence poor perinatal survival,
 ■ Poor perinatal care.

Perinatal care is often very unsatisfactory. When available, it is availed of only by a proportion of the mothers because of illiteracy, ignorance and cultural and social bias.

It is now widely accepted that significant gains as far as IMR are concerned are due to fall in post neonatal deaths as a result of availability of Integrated Child Development Services (ICDS) scheme, usual interstitial pneumonia (UIP), acute respiratory infection (ARI), vitamin A prophylaxis programs, etc. Since perinatal mortality, accounting for 60% of the IMR, remains only marginally altered, it has become increasingly difficult to remove stagnation in the IMR (at present 36). This factor apparently contributed to India's failure to meet the deadline of reducing the IMR to under 60/1000, perinatal mortality to 30 to 35/1000 and incidence of low birth weight infants to 10% from 30% by the year 2000 and meeting the millennium goals by the year 2015.

According to one estimate, chances of a newborn attaining the age of 5 years in India are the same as reaching the age of 50 or 60 years in the prosperous countries. The pre-schoolers form about 17% of the population, but are responsible for over 40% of the total mortality. Notwithstanding the developments of the past decade, under-5 mortality, infant mortality, neonatal mortality and perinatal mortality rates are still unacceptably high. Notably, mortality rates in rural and periurban areas are nearly double of those in urban areas.

HIGH MORBIDITY AND MORTALITY: CAUSE AND SOLUTION

Let us have a peep into the real cause of high morbidity and mortality in children in India.

- Whereas in advanced countries 5–12% of the gross national product (GNP) is reserved for health services, only 2% of India's GNP is allocated for this vital area.
- Maternal and neonatal care, though well accepted, is crying for yet more and solid attention. With the exception of tetanus toxoid prophylaxis, iron-folate tablets, and training of the traditional birth attendants (TBAs), no truly concrete program was indeed available for neonates and pregnant women until end of the 20th century. Of course, situation is gradually beginning to change for the better.

A survey conducted in 1976 by us showed that **93% of the teaching institutes in India are not adequately equipped with neonatal care facilities**. A follow-up survey in 1985 and yet another in 1992–93 showed only marginal improvement in the state of affairs. Another survey conducted by the National Neonatology Forum (India) pointed out that almost 3/4th of the hospitals are not equipped with even the basic tools of neonatal care, like low-reading rectal thermometers, oxygen head boxes, resuscitation equipment, exchange transfusion sets and incubator/open care system. The

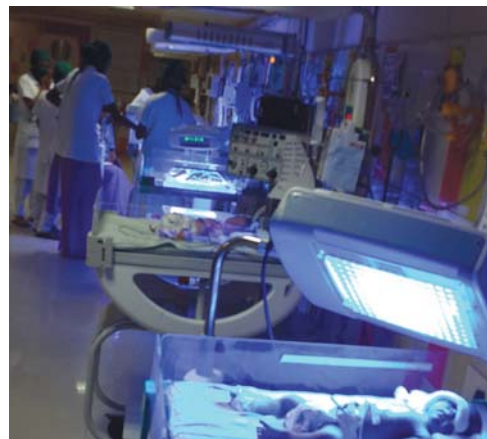


Fig. 1.15: Of late, neonatal care has witnessed considerable improvement in India with opening of neonatal intensive care units in many parts of the country. However, it is by and large limited to the urban sector.

neonate is regarded as only a byproduct of conception. He is seldom entitled to a status of a bed in the ward.

According to the preliminary results of our most recent survey, well meaning child-friendly developments over the last decade or so are beginning to transform the pediatric scenario in the country to one of expectancy. Neonatal care, for instance, has witnessed considerable improvement in India with opening of neonatal intensive care units across the country (Fig. 1.15). However, as yet the development is by and large limited to the urban sector, warranting its extension to the rural sector.

Besides the inadequacy of the health strategy, unfavorable factors like rising population, lack of resources, poverty, ignorance and illiteracy have contributed to the sad state of health of our children.

Logically, therefore, the solution lies in the health services going to them rather than other way around. No wonder that this also requires active participation of the communities which should learn to protect themselves from disease and seek help as and when they need it. There is also need to increase the health budget which at present is inadequate.

MILLENNIUM DEVELOPMENT GOALS AND INDIA'S CHILD CENTRIC INITIATIVES

As duly emphasized by the UNICEF, development begins with the child. Children's welfare measure will lead to every aspect of the development of a nation—economic, social and political. India has fared well in meeting certain child-related development goals.

With this background, in September 2000, India along with 188 other nations signed the United Nations Millennium Declaration, committing to eradicating extreme poverty in all its forms by 2015.

To help track progress toward these commitments, a set of time-bound and quantified goals and targets, called the **MDG**, were developed to combat poor economic status in its many dimensions, including:

- Poverty,
- Hunger,
- Disease,

- Environmental degradation,
- Gender discrimination.

The MDGs include 8 goals, 21 targets and 60 indicators for measuring progress in the 15 years between 1990 and 2015, when the goals were expected to be met.

Unfortunately, now that we are very much in the midst of 2015, except for MDG 4 to **reduce child mortality**, and MDG 5 to **reduce maternal mortality** (which has come down to little over 100/100,000, other MDGs remain unrealized or only partially realized by 2015).

Not that, India has not put efforts to realize these goals. Far from that! recognizing the challenges to meeting the Millennium development goals, the Government has in recent years implemented national flagship programs for education, reproductive and child health, child development, child protection, child nutrition, and water and sanitation. Restructuring and universalizing the ICDS scheme to respond to the challenges in child development has provided great opportunities to speed the pace of progress towards the MDGs, and with a greater level of inclusion.

In fact, historically, the Indian Government has adopted ambitious targets related to children that are in line with, and at times more ambitious than, the MDGs through its five-year plans. Centrally sponsored schemes have increased public resources to key sectors, notably the **Sarva Shiksha Abhiyan** in education—the national policy to universalize primary education, the reproductive and child health program II and the national health mission which now stands extended to include urban poor. The challenge remains to convert these commitments and resources into measurable results for all children, especially those belonging to socially disadvantaged and marginalized communities.

Perhaps, there is a need for rethinking on the part of think-tanks on India's execution of its strategy to deliver health to the people, especially children in a vast country remarkable for diversity and logistic bottlenecks and roadblocks. Let's hope, we successfully fulfill the unmet or inadequately met MDGs.

FETAL ORIGIN OF ADULT DISEASE: A CHALLENGE

The famous Barker's hypothesis, after David Barker (Fig. 1.16), linking the adult diseases to fetal period, now appears to be holding good in entirety (Box 1.4). Evidently, we are in for the fresh challenges.

According to Barker's hypothesis, the impact of impaired intrauterine growth and development does not restrict itself to infancy, childhood and adolescence. Its consequences go much beyond that. In other words, roots of adult disease are laid during fetal life only.

For instance, impaired fetal growth and development (low birth weight, for instance) may well predispose to development of cardiovascular (hypertension, ischemic heart disease, stroke), endocrine (type II diabetes) and metabolic (obesity) diseases during adulthood.



Fig. 1.16: David Barker (1938–2013). A physician and epidemiologist, known for the famous hypothesis after his name, believed in the protection of nutrition of young mothers and babies-in wombs as a safeguard against adult disease.

Box 1.4 Salient features of Barker's hypothesis of fetal origin of adult disease (FOAD)

- A definite association exists between small size at birth or during early infancy and later cardiovascular disease reflecting permanent effect of fetal undernutrition. Fetus adopts to an inadequate nutrition supply by:
 - Prioritization on brain growth at the expense of other viscera,
 - Reduced secretion or sensitivity to fetal growth hormone, insulin and IGF-1,
 - Upregulation of hypothalamic pituitary-adrenal axis.
 These adaptations become permanent or programmed as they occur during critical period of early development. Increased risk of coronary heart disease and stroke associated with low birth weight (LBW) may be minimized through improved weight gain during infancy.
- In intrauterine growth restriction/retardation (IUGR), development of endocrine pancreas is impaired. As a consequence, B-cell mass through aging and insulin resistance and insulin-dependent diabetes could develop. Other changes include:
 - Low muscle mass,
 - Low nephron numbers,
 - Altered arterial structure.
- IUGR of symmetric type attributable to maternal nutrition deprivation in mid pregnancy is associated with vulnerability to syndrome X b (small baby syndrome).
- IUGR of asymmetric type attributable to nutritional deprivation in late pregnancy is associated with increased risk of coronary heart disease in adult life.
- Susceptibility of babies who start off with a LBW to such diseases as diabetes and coronary heart diseases is the result of their being programmed in utero in response to an adverse environment. There may be a compensatory catch-up postnatal growth.
- Muscle structure and function aberration are the major cause of insulin resistance.
- LBW and IUGR are associated with higher levels of risk factors like:
 - Insulin resistance syndrome,
 - Lipid and clotting factors,
 - Cardiovascular dysfunction,
 - Obesity.

During critical periods in early fetal growth and development, there are persisting changes in the body structure and function that are caused by environmental stimuli—the so-called **programming**. This relates to the

- 14 concept of developmental plasticity where our genes can express different ranges of physiological or morphological states in response to the environmental conditions during fetal maturation.

Even today, diseases such as diabetes, hypertension, coronary artery disease, obesity, metabolic syndrome etc., are being increasingly diagnosed not only in adults, but also in young children and adolescents. However, chances are that there may well be yet bigger outbreaks of these preventable diseases in the foreseeable future.

It is a paradox that India, now in the thick of overwhelming problem of under nutrition, is heading for a peculiar situation of epidemic of dual burden of under nutrition on one hand and overweight and obesity on the other hand.

The community needs to be forewarned about the fetal origin of adult diseases. There is a dire need to increase awareness about the impending explosion of epidemics of these diseases. Research and deliberation on the prevention and early diagnosis of these diseases employing simple and affordable strategies is also warranted.

PEDIATRIC EDUCATION

Pediatric education, the art of imparting knowledge about child health, in the resource-limited world cannot be on the same lines as in the developed world since the needs of children in the two worlds are not the same.

- Pediatricians in the West face newer problems like acquired immunodeficiency syndrome (AIDS), fetal anomalies, genetic counseling, adolescent substance abuse, obesity, etc.
- In the developing countries, on the other hand, the priorities are malnutrition, diarrheal disease and infections such as ARI, tuberculosis and intestinal parasitoids, as also low birth weight infants. Training in pediatrics in these countries needs a relatively greater focus on clinical diagnostic skills and affordable therapies rather than on sophisticated investigations and expensive therapeutic modalities.

Currently, thanks to the concerted efforts of the IAP, the sole representative body of India's nearly 25,000 qualified pediatricians and a guardian of the specialty in the country, pediatrics, now holds the status of an independent discipline, both in undergraduate medical teaching and university MBBS examinations. As a result, pediatrics is being taught to the medical students on par with adult medicine, surgery and obstetrics and gynecology. The major beneficiary, directly or indirectly, is undoubtedly our child population.

There is a considerable merit in the suggestion that the growth and development component of pediatrics be introduced in the preclinical years of the undergraduate career.

Today, opportunities for post graduation are available not only in general pediatrics, but also in a few of its subspecialties. It is felt that the Medical Council of India

(MCI) must initiate action to develop uniformly standard curriculum as also uniform system of examination in case of the pediatric postgraduates as well. The task needs to be accomplished in the beginning of the 21st century rather than allowed to catch dust for another few decades.

TOWARDS BETTER TOMORROW

To cut the long story short, the greater attention on the whole child—not just the childhood ailments—can go a long way in promoting family welfare and checking enormous population explosion. As soon as people are convinced that their children are going to survive and grow into healthy adults, the temptation to have too many issues will decline.

The pace of practical implementation of Government's professed policy has got to be drastically accelerated. This needs a political will and commitment rather than sheer slogans and paperwork, as also augmentation of the health budget. There is no place for lopsided priorities.

The best pediatric slogan should be:

Not many, but healthy children, if we are keen on having a happier nation.

Box 1.5 lists some of the significant medical advances that are likely to contribute to mitigating medical problems of children in the developing countries such as ours.

To the conservative reader, this may sound rather premature. But, mind you, what we have in mind is the projected scenario a decade or two ahead.

To conclude, let us modify in context of child health what the celebrated critic and writer, John Ruskin (1819–1900), said over a century ago:

I hold it indisputable that the first duty of a State is to see to it that every child is well-housed, clothed, fed, educated and kept fit.

The time to act is now. Today. Yes, right away!

For, as the poet, Gabriela Mistral, put it (Fig. 1.17):

Many of the things we need can wait. The child cannot. His name is Today. To him we cannot answer tomorrow.

The onus lies on the pediatricians and pediatricians-in-the-making, nay, all professionals involved directly or indirectly in preventive and curative child health care to ensure that each and every child attains his development and potentials in full. This is the key gateway to happy and healthy childhood and adolescence (Fig. 1.18), finally leading to productive adulthood.

Box 1.5

Important medical advances likely to mitigate medical problems of children in India and other developing countries

- Better vaccines, pharmaceuticals and diagnostics,
- Food security through improved agricultural methods, therapeutic foods and alternate energy sources,
- More appropriate public health policies and measures,
- Magic bullet drug delivery system,
- Production of artificial blood,
- Computer chips with genes for mastery of the human proteome,
- More application of gene therapy,
- Enhanced partnership for child health.



Fig. 1.17: The Latin American Nobel Laureate, Gabriela Mistral (1889–1957). who observed many of the things we need can wait. The child cannot. His name is today. To him we cannot answer tomorrow.



Fig. 1.18: Healthy and Happy Children. All endeavors related to pediatrics should aim at healthy and happy children who grow and develop as productive adults useful to themselves, to the families and the community at large.

Multiple Choice Questions

- Spot the wrong observation:
 - Pediatrics now covers the period from conception through adolescence
 - Current infant mortality, neonatal mortality and perinatal mortality rates in India are around 46, 24 and 20, respectively
 - Maternal and neonatal tetanus are close to elimination from India
 - National Health Mission now stands extended to urban areas as well
- Each of the following data about India's 12th Five Year Plan is correct, except:
 - The plan covers the period 2012–17
 - Targets reduction in child undernutrition by 1/4th of the NFHS-3
 - Target reduction in infant mortality rate: 25/1000 live births
 - Target reduction in maternal mortality: 100/100,000 live births
- The date, 14th November, is observed as "Chacha Nehru Day" in India. Which day is observed as "Universal Children's Day"
 - 14th November
 - 1st January
 - 2nd October
 - 30th January
- Which of the following observations about disease pattern and mortality in under-5s is correct?
 - In resource-limited world, predominance of malnutrition, diarrheal diseases and infectious diseases
 - In developed world, predominance of perinatal problems and pneumonias and other infections
 - Three top killers of under-5s in developing regions are the trio of "malnutrition, diarrheal disease and infectious diseases"
 - Though mortality from childhood diarrhea has considerably come down, incidence of diarrhea continues to be high, especially in resource-limited communities
 - All of the above
- According to the gist of the Barker's hypothesis, origin of adult disease dates back to the fetus. Which of the following is not a part of Barker's hypothesis concerning LBW and IUGR?
 - Insulin resistance syndrome
 - Lipid, clotting factors, and cardiovascular dysfunction
 - Obesity
 - Short stature

Answers

1. C 2. B 3. A 4. E 5. D

Clinical Problem-solving

Review 1

The impact of impaired intrauterine growth and development does not restrict itself to infancy, childhood and adolescence. Its consequences go much beyond that. In other words, roots of adult disease are laid during fetal life only.

1. In which way(s) does impaired fetal growth and development (low birth weight, for instance) predispose to development of adult diseases?
2. In which way does obesity in childhood contributes to dual nutritional burden?
3. What is the way out?

Review 2

In India and other resource-limited countries, childhood disease pattern is dominated by malnutrition, diarrheal disease and infections such as acute respiratory infections, tuberculosis, diarrheal diseases and intestinal parasitoids, as also low birth weight infants. The scenario is at variance with that observed in the western world. No doubt, some of the problems such as HIV/AIDS, substance abuse and CAN are common to both set of countries.

1. In which way reorientation of medical education can help in tackling our priority problems?
2. What specific change in undergraduate pediatric education can strengthen the curriculum in favor of better child health knowledge and delivery?
3. Any improvement in postgraduate education?

Answers

Review 1

1. By predisposing to such diseases as hypertension, ischemic heart disease, stroke, type II diabetes, obesity, etc.
2. India is currently the thick of overwhelming problem of undernutrition. The concurrent increasing incidence of overweight/obesity may end up in a situation of epidemic of undernutrition on one hand and overweight and obesity on the other hand.
3. We need to forewarn the community about the fetal origin of adult diseases. Increasing awareness about the impending explosion of epidemics of these diseases is fundamental to the larger issue of safeguard against them.

Review 2

1. Training in pediatrics India and such other countries needs a relatively greater focus on clinical diagnostic skills and affordable therapies rather than on sophisticated investigations and expensive therapeutic modalities.
2. Introduction of growth and development component of pediatrics in the preclinical years of the undergraduate career may well be of considerable help.
3. Medical Council of India (MCI) must initiate action to develop uniformly standard curriculum as also uniform system of examination in case of the pediatric postgraduates as well.

FURTHER READING

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SECTION 2

Core Pediatrics

Section Outline

2. Pediatric History-taking and Physical (Clinical) Examination
3. Normal Growth
4. Growth Disorders
5. Development
6. Developmental, Behavioral and Psychiatric Disorders
7. Adolescent Medicine
8. Pediatric-related Biostatistics
9. Community Pediatrics
10. Immunization
11. Nutritional Requirements
12. Infant and Young Child Feeding
13. Malnutrition
14. Vitamins
15. Micronutrients/Trace Elements/Minerals
16. Fluids, Electrolytes and Acid-base Balance and Disturbances

Pediatric History-taking and Physical (Clinical) Examination

Suraj Gupte, Rita Smith

GOALS

Ever since the time of Hippocrates, history-taking and clinical examination of the child occupies pride of place as a remarkable art. It builds up gradually on a good foundation through repeated exposures, application of knowledge and guided practical experience spread over years and years. Major goals of history-taking and clinical examination are:

- Data collection from history,
- Data collection from physical examination,
- Analysis of the data so obtained,
- Arriving at a provisional clinical diagnosis or most likely probabilities,
- Differential diagnosis,
- Planning investigations to confirm the clinical diagnosis,
- Treatment plan.

THE ART OF HISTORY-TAKING

INFORMANT

The best person to give the history (*informant*) is the mother of the child or someone else responsible for his care. If the child is old enough to communicate information, he should also be interviewed. History obtained from father, uncles, aunts or grandparents, who have not been deeply involved in child care is less reliable.

ENVIRONMENT

As far as possible, history should be taken in a room with minimum of noise and disturbance and an environment that is child-friendly.

APPROACH

The approach to the child as also the informant should be friendly. Let the informant tell the story as she sees it. You may later put leading questions to fill in the gaps and for detailed elaboration. Avoid putting trying and embarrassing questions. Creating a feeling of guilt or shame in the informant's mind will only make your job difficult. Yet, important information has got to be obtained. This may require tactful handling of the situation. At times, it may be more workable to obtain some such information rather later in the interview, during the clinical check-up or even at a subsequent interview.

RECORD

The case-sheet must have a record of clear and precise information about the history in chronological order. Besides

the entries regarding name, age and sex, parents' name and address, etc. the recording should be in the standard order (Box 2.1) with marginal modifications as and when indicated.

BASIC INFORMATION

It includes child's name, sex, parentage and address along with the identity of the informant.

PRESENTING COMPLAINTS

- The first question to be asked is—"Well, what is the main complaint"? This leads the informant to state the problem. Mind you, here reply is to be written down in informant's own words rather than in medical jargons. It is wrong to convert "has not passed urine, since yesterday" to "anuria -1 day". Presenting complaints must be in the informant's own account and must include the duration also.
- Furthermore, the complaints need to be recorded in chronologic order, i.e. in order of occurrence (Box 2.2). One must obtain detailed information about the various complaints such as cough, fever, breathlessness (Table 2.1), vomiting, diarrhea, abdominal pain, hematemesis, bleeding per rectum, appetite, micturition, failure to thrive, swelling (edema), rash, jaundice, cyanosis and pallor, etc. depending on the merits of the case.

Box 2.1 History and physical examination record

- Basic information (child's name, sex, parentage and address along with the identity of the informant)
- Presenting complaints
- History of present illness
- History of past illness
- Birth history
 - Antenatal
 - Natal
 - Perinatal
 - Postnatal
- Developmental history (milestones)
- Dietary history
- Immunization history
- Personal history
- Family history
- Socioeconomic history

Box 2.2 Model of presenting complaints in an 8-month-old infant brought for loose motions

- Loose motions—3 days
- Fever—2 days
- Reduced urine output—1 day
- Increasing drowsiness—2 hours

Table 2.1: Grades of breathlessness (dyspnea) as per New York Heart Association

Grade	Breathlessness
1 (Slight)	Occurring on unaccustomed (more than average), exertion, e.g. running, playing a game (outdoor)
2 (Moderate)	Occurring on ordinary exertion, e.g. walking at normal pace, climbing upto sheer 2 rugs
3 (Considerable)	Occurring even without ordinary exertion
4 (Gross)	Occurring even at rest

HISTORY OF PRESENT ILLNESS

After the chief complaints, you should record the details of the present illness.

- When was the child quite well? How and when did the present problem start?
- Any suck-rest-suck cycle, excessive sweating, excessive crying etc.?
- How was further progression of the main problem? Was it stationary, improving or worsening?
- What were the new symptoms?
- Any aggravating/alleviating factors?
- Pertinent negative data that may have a bearing on the diagnosis?
- Any treatment given?

HISTORY OF PAST ILLNESSES

- How was child's previous health? Make a note of duration, dates and types of various illnesses.
- Also, state if any, treatment was given.
- History of recurrent diarrhea and recurrent sinopulmonary infection with failure to thrive despite good dietary intake is very suggestive of cystic fibrosis.
- Umbilical sepsis in the neonatal period may well be a precursor of portal hypertension later in life.
- Episodes of wheezy bronchitis in the past may well strongly point to the diagnosis of bronchial asthma.

BIRTH HISTORY

One should elucidate the factors that may have bearing on child's health before, during and after birth.

Antenatal

It is important to know about mother's health during pregnancy:

- How was her diet?
- Any history of illnesses such as rubella, syphilis, toxemia, diabetes, hypertension, heart disease, tuberculosis, exposure to radiation, or drug intake?
- Maternal intake of such antiepileptic drugs (AEDs) as phenytoin, valproate and trimethadione may have teratogenic effect on the fetus.
- Any blood group incompatibility between the parents?

Natal

- Was it a hospital or home delivery?
- Who conducted it—a qualified doctor or midwife, or simply an untrained *dai*?
- Was the delivery normal or not?
- What was the baby's birth weight?
- Did he look healthy or sick? Any cyanosis?
- Any respiratory distress? Cry? Was any resuscitation needed?

Postnatal

- Apgar score?
- Any jaundice, cyanosis, convulsions, congenital anomalies, or birth injury noticed during the neonatal period?
- Any resuscitation measures employed after delivery?
- How was the umbilical cord cut? Any pus oozing out of it?
- Any suckling difficulty?
- What was the birth weight?
- Excessive weight loss?
- When was the meconium passed? Absence of meconium passage may point to intestinal obstruction; a passage after 24 hours may suggest cystic fibrosis.
- When was the urine passed? Voiding of urine after 48 hours indicates renal agenesis or an obstruction in the system.

DEVELOPMENTAL MILESTONES

- You must find out when the child gave first social smile and learned head-holding, sitting with and without support, crawling, standing and walking with and without help and talking meaningful words and sentences.
- Any dental eruption and the timing?
- Also ask about control over bowel and bladder, both during the day and night.
- Any regression in milestones? Any period of growth failure or unusual growth should also be elicited.
- It is important to know about school grade and quality of work.

IMMUNIZATION STATUS

- You must ask about the various vaccinations (including the new vaccines, optional vaccines and pulse polio) received by the child with dates (ask for an immunization record card, if available).
- If a certain vaccination has been omitted, find out why.
- Also, ascertain if any vaccination caused some adverse effect the so-called **adverse event following immunization (AEFI)**.

DIETARY HISTORY

- Was the child breast or bottle fed?
- If on formula, how was it prepared? Find out about sterilization of the feeding equipment and whether the dilution of the formula was as recommended or far too much. Any feeding difficulties?

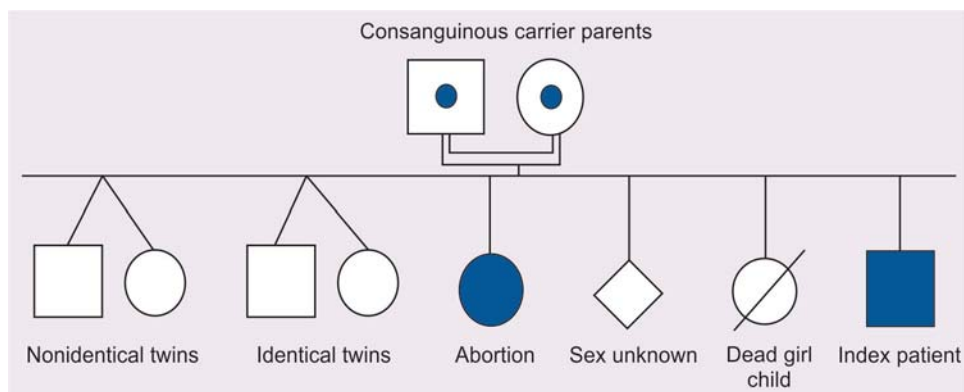


Fig. 2.1: Guidelines for construction of family pedigree (genetic) diagram.

- When were the semisolids and solids introduced? Find out more details about the complementary foods and how they were given and in what quantity.
- When were vitamin and mineral supplements started?
- It is important to provide some details of the current dietary intake.
- Does child's appearance match the mother's story about his intake?
- You must also get information about child's food likes and dislikes. How does he react to eating?
- Any food allergy (cow's milk, egg, soybean)?

PERSONAL HISTORY

- How are child's relations with the siblings, other family members and children in the school?
- Is he a difficult child?
- Does he cling to mother's apron strings? Is he negativistic? Is he outgoing?
- How are his/her eating, sleep, bowel and bladder habits?
- Any history of pica, enuresis, breath-holding, tics, temper-tantrum, etc.?

FAMILY HISTORY

- History of consanguinity (Table 2.2) is important. Closer the proximity of parents in term of blood relationship, the higher is the sharing of the DNA.
- The health status of the siblings, parents and grandparents should be recorded.
- In case of infectious and familial diseases, history of such illness in the family members must be pointedly sought.

Table 2.2: Consanguinity: grading and significance

Degree	Type of union	Significance
1st Degree	Parent, sibling, child.	DNA sharing 50%
2nd Degree	Uncle, aunt, nephew niece.	DNA sharing 25%
3rd Degree	First cousin, grand parent, grand children.	DNA sharing 12.5%

- In inherited disorders, it is advisable to make a family tree (Fig. 2.1). In disorders like Down syndrome, it is good to know the ages of the parents.

SOCIOECONOMIC STATUS

- How much is the family income?
- Occupation of the parents and the housing.
- School and play facilities available for the child.

The most widely employed modified Kuppaswamy scale is given in Table 2.3.

SYSTEM REVIEW

At the end of history recording, it is advisable to review each system in turn so that nothing important is missed (Box 2.3).

THE ART OF PHYSICAL EXAMINATION

PRE-EXAMINATION PREPARATION

Before embarking on physical examination, it is important to get friendly with the child and win his confidence. This can easily be done while one is taking the history from the mother. During this period, you may also make certain observations about the child.

GENERAL EXAMINATION

The infants should be examined while She/he is in mother's lap or over the shoulder. For toddlers and older children, standing, sitting or examination table are fair enough. Neonates and infants in first few months are best examined on the table only.

The dress should be removed bit by bit to overcome resistance from a shy child and to prevent exposure in a chilly weather.

- Physical examination of a child is from region to region. The examiner must first develop a friendly rapport with him. An examination, which is likely to be irritating should be done towards the end.
- The whole of the body from scalp hair to tips of the toes is properly inspected.
- The sequence of examination depends upon the cooperation received from the child.

Table 2.3: Modified Kuppaswamy socioeconomic scale

A. Education	Score
• Professionals or honors	6
• Graduate or postgraduate	5
• Intermediate or post-high school diploma	4
• High school certificate	3
• Middle school certificate	2
• Primary school or literate	1
• Illiterate	1
B. Occupation	Score
• Profession	10
• Semi-profession	6
• Clerical/shop owner/farmer	5
• Skilled worker	4
• Semiskilled worker	3
• Unskilled worker	2
• Unemployed	1
C. Family Income/month (₹)	Score
• 19575 or more	12
• 9788-19574	10
• 7323-9787	6
• 4894-7322	4
• 2936-4893	3
• 980-2935	2
• 979 or less	1
Socioeconomic class	Total score (A + B + C)
Upper	26–29
Middle	
• Upper middle	16–25
• Lower middle	11–15
Lower	
• Upper lower	5–10
• Lower	<5

Box 2.3 System review

- **Ear, nose and throat:** Ear discharge, earache, hearing, stuffy or running nose, postnasal discharge, sneezing, frequent colds, sore throat, mouth breathing, snoring.
- **Teeth:** Eruptions at present, time of first tooth, whether in line with other siblings.
- **Heart and chest:** Breathlessness, cough, expectoration, wheeze, cyanosis, chest pain, palpitations, edema.
- **Gastrointestinal tract (GIT):** Diarrhea, vomiting, constipation, pain abdomen, abdominal lump.
- **Liver:** Jaundice, deep urine, light stools, smells in breath.
- **Genitourinary:** Vaginal discharge, menses, visible anomalies of penis, testis or labia and clitoris, dysuria, polyuria, hematuria, pyuria, enuresis.
- **Neuromuscular:** Headache, dizziness, convulsions, ataxia, muscle or joint pains, postural deformities, paralysis.
- **Endocrine:** Facies, activity, obesity, disturbance of growth, polydipsia, visible goiter.
- **Special senses:** Taste, hearing, vision, smell, pain.
- **General:** Weight loss or gain, easy fatigability, growth curve, puberty, skin changes, temperature sensitivity.

- As a rule, uncomfortable procedures such as examination of throat, ear or rectum should be left to the last. Else, an irritated, panicky child is going to be a difficult subject to examine.

Box 2.4 Infant's cry—as a clue to diagnosis

- A high-pitched shrill cry may suggest meningitis.
- A weak-cry may be the result of grave illness, respiratory muscle weakness or generalized weakness.
- A child in agony because of pain may give a strong cry.
- A child appearing comfortable in the bed or on the table, but irritable in mother's lap, the so-called **paradoxical irritability**, should arouse suspicion of conditions such as poliomyelitis, scurvy, infantile cortical hyperostosis or acrodynia.

- It is also wise to avoid a prolonged examination.
- It is of distinct value to highlight the positive findings and put question marks (?) against the doubtful findings, which may well be crosschecked later.

OVERALL APPEARANCE

- What is the child's level of consciousness (sensorium)—fully conscious, drowsy, in stupor, delirium, or comatose?
- Does the child look acutely sick?
- Is he comfortable, cooperative and interested in the surroundings?
- Is he apprehensive, apathetic or hyperactive?
- Is there any suggestion of a respiratory distress?
- Does he look mentally retarded?
- Does he have any obvious malformation or deformity? Is there anything characteristic about his facial appearance (dysmorphism)?
- Is he wasted, obese or average?
- Note his cry, which may give a clue to the diagnosis (Box 2.4).
- A frog-like posture may mean poliomyelitis or scurvy.

VITAL SIGNS

It is advisable to make a note of vital signs (pulses, respiration and temperature) at this stage (Table 2.4), including their abnormalities.

- **Pulse:** Radioradial delay suggests coarctation of aorta (COA) proximal to the origin of left subclavian artery whereas radiofemoral delay points to COA distal to the origin of left subclavian artery.
- **Respiration:** Make a particular note of respiratory rate, chest retractions (Box 2.5), type of breathing—whether normal or abnormal (Box 2.6) and abnormal sounds (Box 2.7). In infants, breathing is abdominal; in young children, it is abdomino-thoracic; thoracic

Table 2.4: Vital signs

Age group	Pulse/min	Respiration/min	Temperature (°C)/(°F)
Newborn	140	40	36.0 – 37.0/96.8 – 98.6
1 year	120	30	36.5 – 37.5/97.7 – 99.5
5 years	100	20	37 ± 0.2 /98.6 ± 0.5
10 years	90	18	37.0 ± 0.2/98.6 ± 0.5
>10 years	80	18	37.0 ± 0.2 /98.6 ± 0.5

Box 2.5 Significance of chest retractions (indrawing)

- **Subcostal:** Mild distress
- **Intercostal:** Moderate distress—lower respiratory tract disease bronchopneumonia, lobar pneumonia, bronchiolitis.
- **Suprasternal, sternal, supraclavicular:** Severe distress—common in laryngotracheobronchitis (croup).

Box 2.6 Features of abnormal breathing patterns

- **Kussmaul breathing:** Deep breathing occurring in metabolic acidosis.
- **Paradoxical breathing:** Abdomen moving inward (rather than outward) in inspiration, occurring in diaphragmatic paralysis.
- **Periodic breathing:** Alternate periods of rapid breathing followed by apnea (<20 seconds) without bradycardia or cyanosis, occurring in normal neonates.
- **Cheyne-stokes breathing:** Alternate periods of rapid breathing followed by apnea, occurring in older children suffering from raised intracranial pressure (ICP) or heart failure.
- **Biot's breathing:** Apnea followed by 4–5 normal breaths, occurring in raised ICP.

Box 2.7 Types of abnormal respiratory sounds heard without stethoscope

- **Stridor:** Usually an inspiratory sound from an upper airway (larynx, trachea) obstruction.
- **Wheeze:** Audible whistling sound, predominantly expiratory from lower airway (bronchi, bronchioles) obstruction.
- **Grunting:** Expiratory sound against a partially close glottis, occurring in respiratory distress syndrome (RDS).
- **Rattling:** Inspiratory sound from secretions in the airway.
- **Snoring:** Low pitched, irregular, inspiratory sounds from oropharyngeal obstruction.

in older children and adolescents. Presence of “suck-rest-suck” cycle during feeding may be a signal for respiratory block or heart disease.

- **Temperature:** Axilla and groin are the most practical sites for recording temperature in infants in infants and toddlers. In older children and adolescents, mouth temperature is fair enough. Rectal temperature is needed in critically sick and malnourished children who are vulnerable to hypothermia. Normal temperature is 99.7–99.5°F. A temperature beyond 99.5°F is considered fever (Box 2.8).
- **Blood pressure:** BP should be recorded employing an appropriate size cuff that covers 2/3rd of upper arm circumference. BP in a neonate is about 70/45 mmHg. Upto 1 year it moves in the range 70–80/50–60 mmHg. After 1 year:
 - **Systolic BP** = $90 \pm \text{age (years)} \times 2$
 - **Diastolic BP** = $55 \pm \text{age (years)} \times 2$
 BP >95th percentile needs to be considered as hypertension.
- **Capillary filling time:** Capillary filling time (CFT) can be recorded by pressing the skin over forehead, finger pulp, nail bed or sternum for 5 seconds so as to cause blanching. Then pressure is released and time taken

Box 2.8 Types of fever

- **Continuous fever:** Present throughout the day with fluctuation <1°C in 24 hours. Examples: Pneumonia, urinary tract infection (UTI), infective endocarditis
- **Remittent fever:** Present throughout the day with fluctuation of >1°C in 24 hours. Examples: Infective endocarditis
- **Intermittent fever:** Present only during certain periods of the day. In between, temperature is normal. Examples: Malaria, kala-azar, juvenile rheumatoid arthritis.
- **Quotidian fever:** Intermittent fever occurring daily.
- **Tertian fever:** Intermittent fever occurring on alternate days.
- **Quartan fever:** Intermittent fever occurring at 2 days interval.
- **Fever with rigors/chills:** It is encountered in infectious processes such as malaria, UTI, large abscesses, septicemia, etc.
- **Relapsing fever:** Sudden recurring episodes of high fever which usually last from three to seven days, usually caused by a spirochete transmitted by the bite of a body louse or a tick.
- **Undulant fever:** High fever spikes usually occur every afternoon in brucellosis. The name undulant fever is because the fever rises and falls in waves.
- **Pel-Ebstein fever:** A specific kind of fever associated with Hodgkin's lymphoma; being high for one week and low for the next week and so on.

for return of normal color is noted. CFT more than 3 seconds points to poor perfusion, which may be either due to dehydration or shock.

ANTHROPOMETRY

It is essential to obtain child's weight, height or length, weight-for-height, head, chest and mid upper-arm circumferences (MAC) and if possible, skin-fold thickness. In certain instances, it is of value to measure the upper and lower segments and arm span. For details, See Chapter 3 (Normal Growth).

SKIN, APPENDAGES AND MUCOSA

- Note its color for cyanosis (Box 2.9, Fig. 2.2), jaundice (Fig. 2.3), pallor and caroteminemia.
- Any rash. A maculopapular rash is a key feature of measles (Fig. 2.4).
- Any petechiae, pupura, ecchymosis (Fig. 2.5).
- Look for pigmentation.
- Localized bluish spots, usually on the buttocks and the back, are the so-called **Mongolian spots**. They are self limited, having no clinical significance.

Box 2.9 Cyanosis**Definition**

The bluish discoloration of skin and mucous membrane.

Peripheral

It is present only in the periphery, i.e. limbs as a result of exposure to excessive cold, Raynaud's phenomenon, arterial thrombosis, superior vena cava syndrome or traumatic compartment syndrome.

Central

It is present in central regions as a result of pulmonary (cyanotic congenital heart disease), pulmonary (RDS, congenital diaphragmatic hernia, persistent fetal circulation, pneumonia, etc.), hematologic (polycythemia, hypercoagulability, methemoglobinemia, etc) or neurologic (encephalitis, encephalopathy, etc) disease.



Fig. 2.2: Severe cyanosis.



Fig. 2.3: Jaundice. Note yellowish skin and bulbar conjunctiva.



Fig. 2.4: Maculopapular rash in measles.



Fig. 2.5: Ecchymosis. Note the >10 mm size lesions.

- **Café-au-lait spots** (Fig. 2.6) may be associated with phakomatosis.
- Reticular pigmentation may be a feature of megaloblastic anemia or infantile tremor syndrome.
- In Addison disease, the pigmentation usually gives the skin dirty brown color and may also be present at the gum margins and cheeks.
- Skin turgor is lost during dehydration and marasmus.
- In order to elicit pitting edema (Fig. 2.7), greater pressure requires to be applied in children than in adults.

LIMBS AND FEET

These should be examined for any deformity, asymmetry, hemihypertrophy, bow legs, knock-knees, edema (Fig. 2.7) any swelling or limitation of movements of the joints, etc. Do count the digits and the number of fingers and toes. Also, look for incurving of the little finger, syndactyly, simian crease, platenychia or koilonychia (Fig. 2.8), clubbing (Box 2.10, Figs 2.9A and B and Fig. 2.10), and presence, absence or diminution of arterial pulses. It is absolutely within normal limits for many infants to have flat feet and bow legs.

Presence of rashes, petechiae, ecchymoses or specific diseases should also be observed.

While examining the skin, it is appropriate to look for subcutaneous nodules over bony prominences in suspected cases of rheumatic fever or rheumatoid arthritis.



Fig. 2.6: Café-au-lait spots. Six or more spots of >5 mm diameter in prepubertal subjects and >15 mm diameter in postpubertal subjects are usually diagnostic of neurofibromatosis type 1 (Von Recklinghausen disease). Other conditions in which these may be present include McCune-Albright syndrome, Fanconi anemia and Gaucher disease.

LYMPH NODES

Note the location, size, consistency, mobility, tenderness and warmth of lymph nodes, particularly in the suboccipital, preauricular, anterior and posterior cervical (Fig. 2.11), submaxillary, sublingual, axillary (Fig. 2.12), epitrochlear and inguinal regions.

Posterior auricular and suboccipital adenitis may be the result of otitis externa, scalp infection or lice.



Fig. 2.7: Pitting edema. For its demonstration in a child, the examiner needs to put more pressure with the index finger than in adults, especially in doubtful cases. Usually, it is elicited over the dorsum of foot or shin of tibia by putting pressure for 30 seconds. The pit—a depression—should persist for at least 30 seconds.



Fig. 2.8: Koilonychia. Note the spoon-shaped nails, usually a manifestation of chronic iron deficiency anemia (IDA).

Box 2.10 Clubbing: An overview

Definition

Loss of natural angle between the nail plate and nail bed with boggy fluctuation of the nail bed.

Grading

- **Grade 1:** Increased boggy fluctuation of the nail bed.
- **Grade 2:** Obliteration of the natural angle between the nail bed and the nail plate.
- **Grade 3:** Increase in curvature and thickness of the nail plate from above downward and from side to side. Altered prostaglandin metabolism and proliferation of the connective tissue.

Causes

- **Pulmonary:** Bronchiectasis, emphysema, lung abscess, progressive pulmonary tuberculosis, cystic fibrosis, etc.
- **Cardiovascular:** Infective endocarditis, cyanotic congenital heart disease, etc.
- **Gastrointestinal:** Malabsorption states, ulcerative colitis, Crohn disease, multiple polyposis.
- **Hepatic:** Biliary cirrhosis, chronic active hepatitis.
- **Miscellaneous:** Congenital, familial, thyrotoxicosis, Hodgkin lymphoma, syringomyelia.

Clinical elicitation in doubtful cases

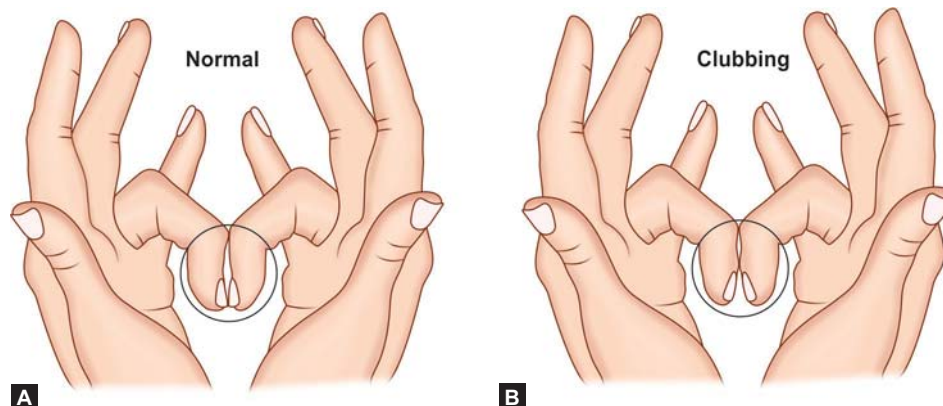
- Depth at the base of the nail equal or greater than the depth at the distal interphalangeal joint.
- Disappearance of the normal window when two fingers are approximated (Figs 2.9A and B).
- When the nail is rocked on its bed with examiner's index finger and thumb, it appears to be floating.

Palpable nodes upto 1 cm in inguinal region and upto 3 mm in rest of the areas may well be passed as within normal limits in healthy children.

HEAD

Occipitofrontal Circumference

It is important to measure the occipitofrontal circumference (OFC) at mid forehead anteriorly and the most prominent part of the occiput posteriorly. At birth, it measures 34–35 cm. Then a gain of 2 cm/month for first 3 months (total gain 6 cm), 1 cm/month in next 3 months (total gain 3 cm) and



Figs 2.9A and B: Clubbing. Note the normal window (left) disappearing in case of clubbing because of the increased amount of soft tissue under the base of the nails (right). The so-called diamond sign or Schromroth sign is quite sensitive for even slight clubbing. Clubbing can also be elicited by rocking the nail on its bed between your finger and thumb. It seems to float.



Fig. 2.10: Clubbing. Note the severe clubbing of fingers and toes in a teenager with infective endocarditis on mitral stenosis.



Fig. 2.11: Cervical Lymphadenopathy. Note enlargement of neck lymph nodes on both sides.

0.5 cm in the subsequent 6 months (total gain 3 cm) occurs. Thus, there is a total gain of 12 cm by the end of the first year when it measures 47 cm. During second and third years, increase is 2 cm and 1.5 cm, respectively. Hence, by 3 years, it is about 50 cm, by 7 years 51 cm and by 12 years 52 at 14 years, it is 53 cm.

Shape

It is important to note the shape whether it is scaphocephaly, oxycephaly (acrocephaly), brachycephaly or plagiocephaly.

Cephalic Index (Cranial Index)

It is the ratio between maximum width and maximum length of the head multiplied by 100, can assist in differentiating



Fig. 2.12: Axillary Lymphadenopathy. Note axillary lymph node enlargement following BCG vaccines. It is usually self-limited.

between different shapes. For instance in scaphocephaly, it is less than 70 whereas in brachycephaly it is more than 80. Also, See Chapter 4 (Growth Disorders) for more details.

Sutures and Fontanels

Since posterior and lateral fontanels close very early in infancy, it is the **anterior fontanel** (Fig. 2.13) that has clinical significance. It is rhomboid-shaped, measuring (from midpoint of a side to midpoint of opposite side) 20 ± 10 mm at birth. It usually closes between the ages of 9 to 18 months. Early-closure suggests craniosynostosis and late closure rickets, congenital hypothyroidism, malnutrition, hydrocephalus, syphilis, etc.

A truly **bulging anterior fontanel** suggests raising intracranial tension or pseudotumor cerebri. A depressed fontanel is a sign of significant dehydration.

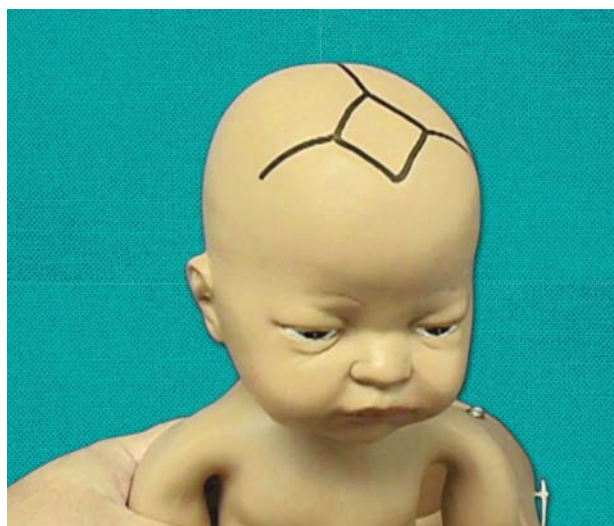


Fig. 2.13: Anterior fontanel. Its patency beyond 18 months, bulging or depression has clinical bearing.

Complete ossification of the **sutures** occurs in late childhood only, though in 6 months these are closed. A palpable ridge over the suture site suggests premature closure as in craniosynostosis. On the other hand, in hydrocephalus, sutures may be separated.

Wormian bones, i.e. soft areas in the occipital region, may suggest the diagnosis of osteogenesis imperfecta, cleidocranial dysostosis, lacunar skull, cretinism or Down syndrome.

Craniotabes, abnormal softening and thinning of skull bones, may be demonstrated by pressing the occipitoparietal area of skull with the thumb. An indentation (sort of a “give”) as in a ping-pong (table-tennis) ball results. Craniotabes may be present in prematurity, rickets, syphilis or osteogenesis imperfecta.

Bruit, an intracranial sound of venous or arterial origin on auscultation, particularly in the temporal region, may well be a normal finding or evidence of an aneurysm or facial hemangioma.

Transillumination is indicated in cases of hydran-cephaly. It is best done in a darkroom. Positive crack-pot or Macewen sign on percussing the skull with a finger does not always suggest hydrocephalus. It may well be positive normally as long as the fontanels are open.

While examining the head, you should also inspect the hair for color, texture, sparseness and easy pluckability. Light-colored, sparse, silky or coarse, easily pluckable hair is usually seen in kwashiorkor, infantile tremor syndrome (ITS) and, sometime, in acrodermatitis enteropathica. Localized alopecia without any sign of infection is seen in trichotillomania. With the presence of infection and pruritic lesions, it should suggest ringworm.

FACE

It should be examined for expression, asymmetry, paralysis, bridge of nose, hypertelorism/pseudohypertelorism, distribution of hair, size of the maxilla and mandible and tenderness over sinuses.



Fig. 2.14: **Facies in Down syndrome.** Note the epicanthal fold, mongoloid slant, flat bridge of nose and microcephaly.

Dull and expressionless faces are commonly seen in mental retardation. So characteristic are the faces in such disorders as Down syndrome (Fig. 2.14), congenital hypothyroidism (Fig. 2.15), chronic hemolytic anemia (Fig. 2.16), adenoids (Fig. 2.17) and gargoylism (Hurler/Hunter syndrome) that a well conversant observer is often in a position to make the diagnosis from a distance.

EYES

One should examine the eyes for photophobia, visual acuity, mongoloid slant, anti-mongoloid slant, epicanthal folds, Brushfield spots, exophthalmos or enophthalmos, pupils, cataract, corneal opacities, squint, nystagmus, xerophthalmia and Kayser-Fleisher ring around the iris. Ophthalmoscopy is important in selected cases.

NOSE

It should be examined for patency, discharge, bleeding, deviated septum, flaring of nostrils, foreign body, polyp and depressed bridge.

MOUTH AND THROAT

Note any unusual shape, cleft lip, nevi, lesions at the corners, ulcers on the buccal mucosa, tongue or pharynx, spongy gums, dental caries or malocclusion, opening of the Stensen duct at the level of second upper molar, Koplik spots, hard and soft palate, tonsils and postnasal discharge.

If a baby can move his tongue over the alveolar margin (which is invariably the case), the so-called **tongue-tie** is out. Strawberry tongue (Fig. 2.18) is seen in Kawasaki disease and Scarlet fever. Fissuring of the tongue occurs in many cases of Down syndrome. Tremors may suggest Werdnig-Hoffmann disease. Frenular ulcer is a feature of pertussis.

Macroglossia may be encountered in cretinism, and gargoylism. Glossoptosis occurs in association with micrognathia and cleft palate in Pierre-Robin syndrome. The throat should be examined for tonsils (Fig. 2.19) and adenoids.



Fig. 2.15: **Facies in congenital hypothyroidism.** Note the dull and coarse facial appearance with large-sized protruding tongue and flat nose.



Fig. 2.16: Hemolytic facies. Note the characteristic frontal bossing, flat nose, prominent maxilla and open mouth with maloccluded teeth. Thalassemia major is the most frequently encountered chronic hemolytic anemia in India.



Fig. 2.17: Adenoid facies. Note the long, dull-looking face with open mouth to facilitate mouth breathing which becomes a necessity on account of posterior nasal obstruction from hypertrophied lymphoid tissues in the nasopharynx. The most dangerous symptom is sleep apnea.



Fig. 2.18: Strawberry tongue. It is characteristically seen in Kawasaki disease and scarlet fever (the latter is rare in India).



Fig. 2.19: Enlarged tonsils. When quite large, it is the common cause of obstructive sleep apnea.

EARS

You must note the shape, size and position of the ears i.e. whether low-set (Fig. 2.20). Deformities may well be a pointer that kidney anomalies are also present. Low-set ears may be associates of other congenital anomalies seen in certain syndromes such as Treacher-Collins syndrome, Apert syndrome, Carpenter syndrome, or Noonan syndrome. Such an ear lies below an imaginary line joining the lateral angle of the eye to the external occipital protuberance.

It is useful to examine the eardrum. Mastoid bone should be percussed for tenderness. Hearing should also be tested. A valuable bedside test consists in observing an infant's response to sound. In normal hearing, he turns his head in the direction of the sound.

NECK

Neck is examined for head holding, swelling (Fig. 2.21), torticollis, jugular venous pressure (JVP) in Figure 2.22, sinuses or fistulas. Any webbing, bull neck or position of trachea should also be noted.

THE ART OF SYSTEMIC EXAMINATION

CHEST

The size, shape and symmetry are carefully examined. A special note should be made about the presence of any retractions (Fig. 2.23), rachitic rosary, pigeon chest deformity, funnel chest and gynecomastia, etc. In examination of lungs, it is important to note the type of breathing, dyspnea and chest expansion, cough, vocal dullness, percussion note, breath sounds, crepitations, and wheeze, etc. Remember that in young children, breathing is mainly abdominal. Table 2.5 gives the significance of certain observations in examination of respiratory system.

HEART

One should examine the heart for location of apex beat, its intensity, precordial bulging, thrills, size, shape, sounds, murmurs and friction rub, etc. Remember that heart should be examined while the child is erect, recumbent



Fig. 2.20: Low-set ears. Such an ear lies fairly below the imaginary line joining the outer canthus with the occiput. Important conditions include Down syndrome, Turner syndrome, Noonan syndrome, DiGeorge syndrome (only unilateral), Edward syndrome, Cri du chat syndrome and Patau syndrome. In the infant shown here, additionally, the ear is grossly deformed.



Fig. 2.21: Goiter in an adolescent girl. This is the most common cause of hypothyroidism in India.

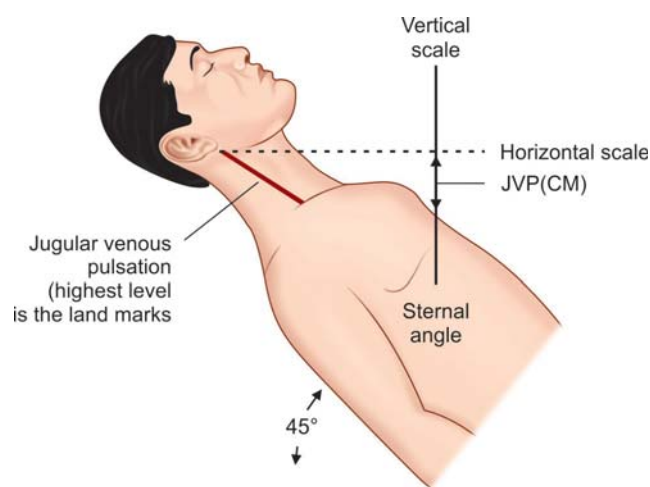


Fig. 2.22: Measurement of Jugular venous pressure (JVP).

and turned to leave. The extrasystoles may also be heard in many normal children. Likewise, sinus arrhythmia may be a normal finding in childhood. Cardiac examination must in particular be very careful, noting the presence of a precordial bulge, substernal thrust, apical heave or a hyperdynamic precordium, thrills (both systolic and diastolic) and aortic bruits, etc.



Fig. 2.23: Chest retractions. This is a common finding in lower respiratory infections such as pneumonia and bronchiolitis.

Auscultation

Auscultation of the precordium requires patience, first concentrating on the characteristics of the individual heart sounds and then on the murmurs.

Heart Sounds

An accentuated or loud first heart sound over the mitral area suggests tachycardia, hyperkinetic heart syndrome, hyperthyroidism or mitral stenosis. In mitral regurgitation and myocarditis, the first heart sound over the mitral area is particularly faint. In tricuspid atresia, the first heart sound over the tricuspid area is accentuated or loud. The second sound is split little beyond the peak of inspiration; it closes with expiration. A wide splitting is encountered in pulmonary stenosis, tetralogy of Fallot, atrial septal defect, and total anomalous venous return and Ebstein anomaly. A narrow splitting points to pulmonary hypertension. The third sound is best heard with the bell at the apex in mid-diastole, especially if the child assumes a left lateral position. It is of significance in the presence of signs of congestive cardiac failure and tachycardia in which situation it may merge with the fourth sound. The latter, coinciding with atrial contraction, may be heard a little before the first sound in late diastole. The phenomenon of poor compliance of the ventricle with an exaggeration of the normal third sound associated with ventricular filling is termed **gallop rhythm**.

After the heart sounds, attention should be focused on clicks. Aortic systolic clicks, best heard at the left lower sternal border occur, in aortic dilatation as in aortic stenosis, tetralogy of Fallot, or truncus arteriosus. Pulmonary ejection clicks, best heard at the left midsternal border, occur in pulmonary stenosis. In prolapse of the mitral valve, a mid-systolic click precedes a late systolic murmur at the apex.

Table 2.5: Significance of certain findings in respiratory system examination

Observation	Significance
Respiratory rate >60/minute (newborn)	Tachypnea
Working of accessory muscles like ala nasi	Respiratory distress
Stridor obstruction	Upper airway (supratracheal) inspiratory
Grunting	Lung parenchyma disease (pneumonia), HMD
Wheezing	Expiratory obstruction (asthma)
Moderate tachypnea with chest retraction	Parenchyma disease (pneumonia), HMD
Marked tachypnea without chest retraction aspiration in the Silent dyspnea, inability to phonate, paradoxical/seesaw breathing	Bronchial disease (asthma), meconium newborn
Severe tachypnea but no manifestations of respiratory disorder	Metabolic acidosis
Peripheral cyanosis	Moderate oxygen desaturation
Central cyanosis	Extreme oxygen desaturation
Clubbing	Chronic hypoxia
Increased tactile vocal fremitus (TVF)	Pneumonia, pure pleural effusion
Decreased TVF	Pneumothorax, pleural effusion with underlying collapse
Harrison sulcus	Chronic airway obstruction (asthma)
Chest tenderness	Emphysema
Hyperresonant note	Emphysema, pneumothorax
Hyporesonant note	Collapse/consolidation
Stony dull note	Pleural effusion
High-pitched bronchial breathing	Consolidation
Low-pitched bronchial breathing	Cavity
Post-tussive suction	Cavity
Succession splash	Hydropneumothorax
Pleural rub	Pleuritis
Fine crepitations (crackles)	Alveolar lesion
Coarse crepitations (crackles)	Bronchial lesion
Rhonchi (wheeze)	Bronchospasm, bronchial obstruction
Conducted sounds	URI, laryngomalacia
Signs of pneumonia anteriorly and in upper half	Upper lobe pneumonia
Signs of pneumonia anteriorly and in middle half	Middle lobe pneumonia
Signs of pneumonia posteriorly	Lower lobe pneumonia
Clinical signs defying any pattern	Mediastinal tumor

Abbreviations: TVF, tactile vocal fremitus; URI, upper respiratory infection; HMD, hyaline membrane disease.

Murmurs

Murmurs need to be described as to their timing, intensity, pitch, area of highest intensity and transmission. Whether

a particular murmur is just functional (innocent with no significance) or has a pathological origin (congenital heart disease) must be decided. Murmurs are audible sounds arising from the flow of blood through blood vessels, valves or heart chamber evincing turbulence. In children, because of closeness of the heart to the thin chest wall, murmurs are relatively more easily heard. As a rule, narrower the blood vessel or opening, or higher the turbulence of flow, louder is the murmur. Murmurs are usually classified as systolic, diastolic, and continuous.

Systolic Murmurs

It may be ejection, pansystolic or late systolic murmurs.

- An **ejection systolic murmur** rises to a crescendo in midsystole. It is, as a rule, coarse. Examples of such murmur are aortic stenosis, aortic coarctation, pulmonary stenosis and atrial septal defect.
- A **pansystolic murmur** occurs all through systole. It is caused by the flow of blood through a septal defect (ventricular septal defect) or an incompetent mitral or tricuspid valve (mitral incompetence), tricuspid incompetence, or a patent ductus arteriosus.
- A **late systolic murmur** is heard well beyond the first sound and stretches to the end of systolic phase (mitral valve prolapse). According to intensity, systolic murmurs are categorized into six grades (Table 2.6).

Diastolic Murmurs

- High-pitched blowing along the left sternal border, indicating aortic insufficiency or pulmonary valve insufficiency.
- Early short, lower-pitched protodiastolic along the left mid and upper sternal border, indicating pulmonary valve insufficiency or after repair of pulmonary outflow tract in such conditions as tetralogy of Fallot.
- Early diastolic at the left mid and lower sternal border, indicating an atrial septal defect or atrial valvular stenosis.
- Rumbling mid-diastolic at the apex after the third heart sound, indicating large right to left shunt or mitral insufficiency.
- Long diastolic rumbling murmur at the apex with accentuation at the end of diastole (presystolic), indicating anatomical mitral stenosis.

Table 2.6: Six grades of systolic murmurs (Keek's classification)

Grade	Characteristics
1	Faintest, requiring very careful auscultation in noise free environments (consultant's murmur); innocent.
2	Soft though slightly louder; usually innocent.
3	Moderately loud without a thrill; may be innocent or organic.
4	Loud, accompanied by a thrill; always organic.
5	Very loud, accompanied by a thrill; still needs stethoscope in contact with chest; always organic.
6	Loudest possible, accompanied by a thrill heard with stethoscope not necessarily in contact with the chest; always organic.

Continuous Murmur (Machinery Murmur)

- It is a systolic murmur, best heard over the second and third left parasternal spaces, that extends into diastole.
- It indicates a patent ductus arteriosus.
- It must be differentiated from a pericardial friction rub, as also from a venous hum.

Remember, over 30% children may have a murmur without significant hemodynamic abnormalities. Typically, the so-called **innocent murmur** is heard in the age group 3 to 7 years, occurs during ejection, is musical and brief, is attenuated in the sitting position, and is intensified by pyrexia, excitement and exercise. As the child grows, such a murmur shows a tendency to be less well heard and may regress fully.

It is of help to apply the time-honored Nada's criteria for presence of heart disease in suspected cases See Chapter 27 (Pediatric Cardiology).

ABDOMEN

It is helpful to bear in mind the anatomic topography (Fig. 2.24) and to examine the abdomen when it is relaxed, i.e. when the infant is taking his feed or sucking at the sugar tip, the mother's lap or shoulder (when the child is struggling and abdomen can be examined from the back) are the best place for abdominal examination. An important tip is to do palpation only when the child breathes and abdomen is relaxed (ballotment method). Note its size and contour, distention, movement with respiration, visible peristalsis, umbilicus, hernias, local or rebound tenderness, palpable organ or lump, hyperresonance, shifting dullness, alteration in bowel sounds, etc. Gentle palpation is of greater value than deep, particularly in the case of spleen. Secondary umbilical hernia is common during first 2 years of life and usually regresses spontaneously.

Palpability of liver should be determined in both the midline and the right nipple line. As a rule, liver is normally palpable upto 2 cm below the costal margin until age 4 years. Therefore, rather than just palpability of liver, it is more reliable to measure the liver span (distance between upper margin of liver dullness and lower edge of liver in the midclavicular line). Normal liver span is 4.5–5.0 cm at

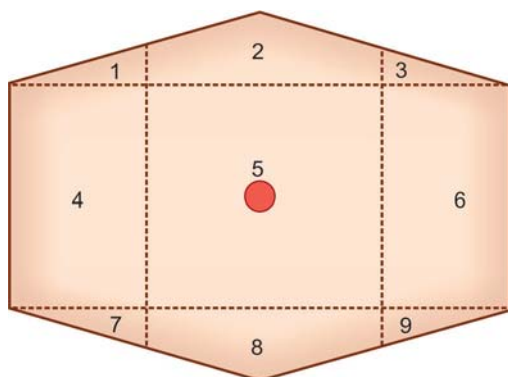


Fig. 2.24: Anatomic topography of abdomen. Region 1, represents right hypochondrium; 2, epigastrium; 3, left hypochondrium; 4, right lumbar; 5, umbilical; 6, left lumbar; 7, right iliac; 8, hypogastrum; 9, left iliac.

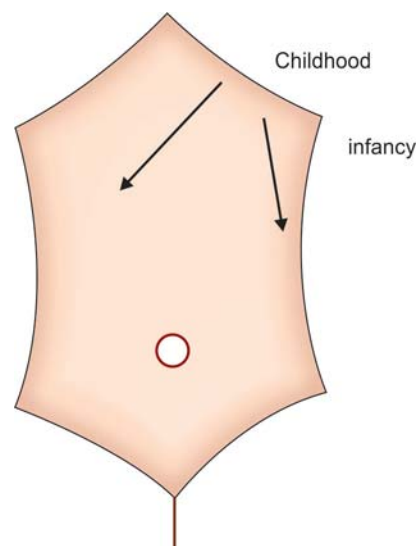


Fig. 2.25: Direction of splenic enlargement. Just palpable spleen is a normal finding in 35% term infants, 10% infants at 1 year and in an occasional child thereafter.

1 week. By 12 years, it goes upto 6.0–6.5 cm in girls and 7.0–8.0 cm in boys.

The tip of spleen is palpable, far more laterally in infants and young children than in older children (Fig. 2.25). In infants until the age of 2–3 months, spleen may be normally palpable.

Splenic size may be graded employing Hagerty's grading (Figs 2.26 and 2.27 and Table 2.7).

GENITALIA

In case of male genitalia, look for circumcision, urethral (meatal) opening, hypospadias, phimosis, paraphimosis, hydrocele, hernia, and undescended testes. Make sure you have warmed your hands before you begin to examine the testes. In case of female genitalia, examine the urethral opening, vagina, hypertrophy of clitoris, and labia minora and majora. Avoid digital or speculum examination.

PERIANAL AND RECTAL EXAMINATION

Note any anal fissure, polyp, prolapse, or perianal erythema (Fig. 2.28).

Rectal examination (restricted to only select situations) should be done with a little finger that is gloved and lubricated with petroleum jelly. Once the finger is on, you may assess the anal muscle tone. Note if the rectum is empty or full. The glove should be examined for feces, mucus and blood after the finger is withdrawn.

SPINE AND BACK

Look for scoliosis (Fig. 2.29), kyphosis, lordosis, dimples, sinuses, spina bifida, tufts of hair, stiffness of neck and back, any swelling and Mongolian spots or tenderness. It is helpful to watch child's gait. Remember that lumbar lordosis together with potbelly may well be a normal observation in the second year of life.

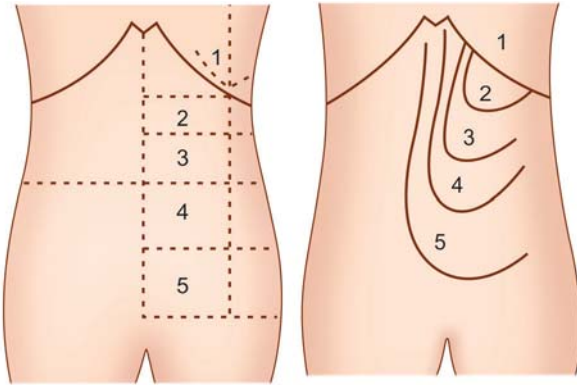


Fig. 2.26: Grading of splenic size.

Table 2.7: Hagerty's grading of splenic size

Grade	Splenic size
1	Normal, not palpable even on deep inspiration
2	Palpable just below costal margin, usually on deep inspiration.
3	Palpable below costal margin, but not projected beyond a horizontal line halfway between costal margin and umbilicus. This projection needs to be ascertained along a line dropped vertically from the left nipple.
4	Lowest palpable points approaching the umbilical level but not below a line drawn horizontally through umbilicus.
5	Lowest palpable points below umbilical level, but not projected beyond a horizontal line situated halfway between umbilicus and symphysis pubis.
6	Lowest palpable point beyond lower limit of grade 5.

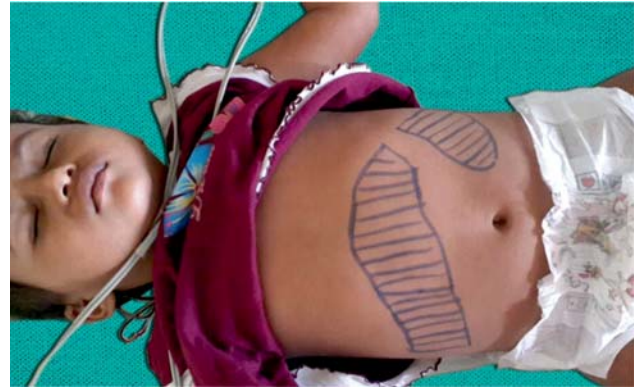


Fig. 2.27: Hepatosplenomegaly. Note the enlarged liver and spleen in a child under treatment for complicated (severe) malaria.



Fig. 2.28: Perianal erythema. It may be due to lactose intolerance, pinworm infestation, wet diaper, poor local hygiene, etc. It predispose to superadded infection, including candidiasis.

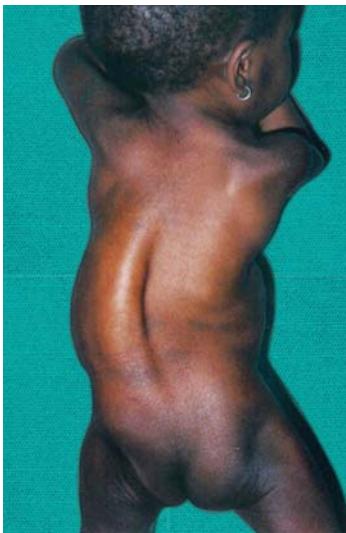


Fig. 2.29: Scoliosis. Note the lateral curvature of spine in a child with severe rickets.

THE ART OF NEUROLOGICAL EXAMINATION

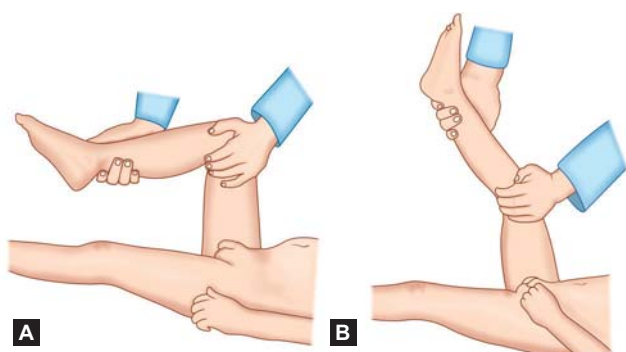
Central nervous system (CNS) examination of an infant or a young child frequently poses difficulties. This is particularly true in the case of sensory examination. Table 2.8 summarizes the special features of CNS examination of infants and children.

Evaluation of cerebral function, cranial nerves (Table 2.9) and their integrity, cerebellar function, motor system, meningeal signs (Figs 2.30 to 2.32) and involuntary movements should be done as and when indicated.

In the case of a newborn, it is important to assess the primitive reflexes *See* Chapter 17 (Neonatology). An estimate about the developmental and mental age should be made *See* Chapter 5 (Development).

Table 2.8: Special features of neurologic examination of infants and children

- A considerable information can be obtained by carefully watching and interacting with the child during history taking and while he is moving about or playing.
- The sense of touch or pain should be tested during the rest of the examination or during play. "Let's play. Close your eyes and say yes when you feel the touch," should be the examiner's approach. Avoiding testing for pain without first preparing the child for it.
- Muscle tone is well tested by lifting the child by the shoulders. A child with generalized hypotonia simply slips out of the hands. The second useful test is that such a child's elbows are able to cross midline of the chest easily (scarf sign).
- The signs of meningeal irritation may be absent in certain situations, say infancy, gross malnutrition, toxemia and septicemia.
- It is usual for the tendon reflexes to be exaggerated (brisk) in young children.
- Primitive plantar reflex may normally persist well upto 1 year. Its prolonged persistence, say beyond 2 years, must be considered abnormal.
- A positive Macewen sign (cracked pot sign) in first 3 years of life may well be normal.
- As a rule, optic disc on fundoscopy appears rather pale even in normal children. Ignoring this fact may lead to overdiagnosis of optic atrophy.



Figs 2.30A and B: (A) Kernig sign. The hip and knee are flexed to a right angle. Then, the leg is gradually extended. Tightness of the hamstring and pain limitation of movements indicates a positive sign; **(B) Brudzinkski sign.** Reciprocal flexion of the contralateral knee during this maneuver indicates a positive Brudzinkski sign.



Fig. 2.31: Cerebral palsy. The child had diplegia (spasticity more marked in lower limbs) and comorbidities, especially low IQ, epilepsy and speech problems.



Fig. 2.32: Decerebrate posturing. Note the extension posturing in a child with tuberculous meningitis stage 3. In decorticate posturing, on the other hand, it is flexion posturing.

Table 2.9: Pediatric testing of cranial nerves

- **First (Olfactory nerve):** Ask the child to close eyes. Find out the odors (say peppermint, orange, lemon, coffee or tea) he is familiar with. Then test for them.
- **Second (Optic nerve):** Test vision and do fundoscopy to watch the optic disc.
- **Third (Oculomotor nerve):** Ask the child to follow a bright object or light in all directions without rotating the head. Watch any limitation. Also watch for size of the pupil.
- **Fourth (Trochlear nerve):** Watch for downward movement of the eye in particular which is impaired in its involvement. Even at rest, the eye tends to move upward.
- **Fifth (Trigeminal nerve):** Test sensation over forehead, cheek and lower jaw. Also, test for corneal reflex and jaw jerk.
- **Sixth (Abducent nerve):** Test for lateral movements of the eye. In its involvement, the child fails to move his laterally (temporally). At rest too, such an eye has a tendency to move medially (nasally).
- **Seventh (Facial nerve):** Test for asymmetry of the face when child is asked to smile or laugh, show teeth, close the eyes and attempt wrinkling the forehead. Whistling too fails in its paralysis. In case of upper motor neuron lesion (supranuclear paralysis), forehead involvement is not elicited.
- **Eighth (Vestibulocochlear nerve):** For auditory component, test or deafness or ringing in ears. For vestibular component, test for positional nystagmus.
- **Ninth (Glossopharyngeal nerve):** Test for gag reflex on touching child's posterior pharynx with a tongue depressor.
- **Tenth (Vagus nerve):** Examine throat for position of uvula. The normal midline uvula turns to the healthy side in case of unilateral involvement.
- **Eleventh (Spinal accessory nerve):** Ask the child to shrug shoulders which showing drooping in its involvement. Moreover, he fails to move head away from the affected side.
- **Twelfth (Hypoglossal nerve):** Ask the child to show the tongue which is deviates to the involved side. The speech of the child too becomes thick.

A SAMPLE (MODEL) PEDIATRIC CASE SHEET

- | | |
|-----------------------------------------|-------------------------------------------------|
| ■ Child's name _____ | ■ Final diagnosis _____ |
| ■ Age _____ | ■ Suggested follow-up _____ |
| ■ Sex _____ | ■ Any other remarks _____ |
| ■ Reg. no _____ | ■ Informant and his/her reliability _____ |
| ■ Father's name and occupation _____ | ■ Chief complaints (in chronologic order) _____ |
| ■ Full address _____ | ■ History of present illness _____ |
| ■ Phone/mobile no/e-mail ID _____ | ■ History of past illnesses birth history _____ |
| ■ Date of admission _____ | ■ Antenatal _____ |
| ■ Date of discharge _____ | ■ Natal _____ |
| ■ Provisional clinical impression _____ | ■ Postnatal _____ |

SALIENT DEVELOPMENTAL MILESTONES

- | | |
|-------------------------|----------------------------------------|
| ■ Social smile _____ | ■ Pincer |
| ■ Head-holding _____ | • Immature _____ |
| ■ Sitting | • Mature _____ |
| • With support _____ | ■ Walking |
| • Without support _____ | • With support _____ |
| ■ Standing | • Alone _____ |
| • With support _____ | ■ Speech |
| • Without support _____ | • Monosyllables _____ |
| ■ Crawling | • Bisyllables _____ |
| • On hands _____ | ■ Bacillus Calmette-Guerin (BCG) _____ |
| • On hands-knees _____ | |

IMMUNIZATION STATUS

- | | |
|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| ■ Oral polio virus (OPV) _____ | ■ Dietary history _____ |
| ■ Hepatitis B _____ | ■ Give rough estimate of intake by recall method before and during illness. Comment on adequacy. |
| ■ Triple diphtheria, pertussis and tetanus (DTP) _____ | ■ Personal history _____ |
| ■ Human immunodeficiency virus (HIV) _____ | ■ Family history _____ |
| ■ Pneumococcal _____ | ■ Socioeconomic status _____ |
| ■ Rota virus vaccine _____ | ■ General remarks (appearance, etc) (-%): |
| ■ Measles mumps and rubella (MMR) _____ | • Head _____ |
| ■ Typhoid _____ | • Weight (-%) _____ |
| ■ Hepatitis A _____ | • Height/Length circumference _____ |
| ■ Chickenpox _____ | • Mid-arm circumference (-%) _____ |
| ■ Meningococcal _____ | • Chest circumference _____ |
| ■ Human papilloma virus (HPV) _____ | • Muscle status skin-fold _____ |
| ■ Any other: _____ | |
| ■ When were primary and booster /recall/ repeat doses given? If not given, why? | |

GENERAL PHYSICAL EXAMINATION*

- General remarks (appearance, etc) _____
- Anthropometry _____
- Weight _____
- Length/Height (preferably with U/L segment ratio) _____
- Weight for height _____
- Head circumference _____
- Mid-upper arm (MUAC) circumference _____
- Chest circumference _____
- Skin-fold _____

MUSCLE STATUS: GENERALIZED OR SELECTIVE WASTING

- Anterior fontanel _____
- Dermatoses _____
- Pallor _____
- Cyanosis _____
- Jaundice _____
- Clubbing _____
- Temperature _____
- Pulse/heart rate _____
- Respiratory rate _____
- Clubbing _____
- Lymphadenopathy _____
- Koilonychia/platonychia _____
- Edema/puffiness _____
- Any vitamin deficiency signs _____
- Any other finding _____

SYSTEMIC EXAMINATION

- Respiratory system _____
- Cardiovascular system _____
- Abdomen _____
- Central nervous system (CNS) _____
- Musculoskeletal system _____
- ENT _____
- Eyes _____

SUMMARY OF THE CASE

- **Provisional clinical diagnosis** _____
- **Discussion** _____
(Please give important points in support of your clinical impression. Also comment on the differential diagnosis).
- **Investigations** _____
(You would like to do) _____
- **Progress notes** _____
(Brief record of investigations done, treatment given from time to time and patient's progress in the hospital)

* Physical examination of a child is from region to region. The examiner must first develop a friendly rapport with him. Examination which is likely to be irritating should be done towards the end. Furthermore, it is of distinct value to highlight the positive findings and put question mark (?) against the doubtful findings which may well be cross-checked later.

Multiple Choice Questions

- Spot the wrong observation:
 - Third degree consanguinity denotes union with first cousins, grandparents and grandchildren
 - Maternal intake of phenytoin, valproate or trimethadione may explain the presence of malformations in the neonate
 - Posterior auricular and suboccipital adenitis may be the result of otitis externa, scalp infection or lice
 - Rectal rather than mouth or axillary/groin temperature is a must in most children
- Each of the following statements is correct, except:
 - Stridor is usually an inspiratory sound from an upper airway (larynx, trachea) obstruction
 - Grunting is an inspiratory sound against a partially closed glottis, characteristically occurring in respiratory distress syndrome in newborns
 - Rattling is an inspiratory sound from secretions in the airway
 - Snoring is a low pitched, irregular, inspiratory sounds from oropharyngeal obstruction
- Causes of posterior auricular and occipital lymphadenitis include each of the following, except:
 - Mumps
 - Otitis externa
 - Scalp infection
 - Head louse
- A bruit, an intracranial sound of venous or arterial origin on auscultation, particularly in the temporal region of the head, may be:
 - A normal finding
 - Evidence of an aneurysm
 - Evidence of a facial hemangioma
 - Evidence of pseudotumor cerebri
- Light-colored sparse scalp hair is a feature of each of the following, except:
 - Kwashiorkor
 - Infantile tremor syndrome
 - Trichotillomania
 - Acrodermatitis enteropathica
- True about the conditions with which low-set ear(s) is associated:
 - Trisomy 21, 18 or 13
 - Turner syndrome
 - Cri du chat syndrome
 - All of the above

Answers

1. D 2. B 3. A 4. D 5. C 6. D

Clinical Problem-solving

Review 1

A student is in for facing music for presenting a pediatric case in a haphazard manner, and then arguing "that is how in adult medicine, we proceed". Indeed, physical examination of the child, as is well known, cannot be on the same lines as that of an adult. Furthermore it must follow pre-examination preparedness.

- What should be the sequence of general examination?
- What is preferred: System-to-system examination or region-to-region examination?
- What's pre-examination preparedness?

Review 2

General physical examination of the child should take a special notice of such items as breathing, fever, pulse, sensorium, irritability, etc.

- What's the difference between Cheyne Stokes breathing and Kussmaul breathing?
- What is the normal BP in neonates?
- What's paradoxical cry?

Answers

Review 1

- The sequence of examination depends upon the cooperation received from the child. Uncomfortable procedures such as examination of throat, ear or rectum should be left to the last. Else, an irritated, panicky child is going to be a difficult subject to examine.

contd...

2. Physical examination of a child is from region to region.
3. The core of such preparedness is getting friendly with the child and win his confidence. This can easily be done while one is taking the history from the mother. During this period, the examiner should make any observations the child is manifesting such as any dysmorphism, change in sensorium, conduct, attention, etc. Such observation will stand the examiner in good stead when he subsequently embarks on complete examination.

Review 2

1. The term, Cheyne Stokes breathing, denotes alternate periods of rapid breathing followed by apnea, occurring in older children suffering from raised intracranial pressure (ICP) or heart failure. It should be considered "normal" in case of neonates.
The term, Kussmaul breathing, refers to deep breathing occurring in metabolic acidosis.
2. BP in a neonate is about 70/45 mmHg. Upto 1 year it moves in the range 70–80/50–60 mmHg.
3. A child appearing comfortable in the bed or on the table, but irritable in mother's lap, the so-called **paradoxical irritability**, should arouse suspicion of conditions such as poliomyelitis, scurvy, infantile cortical hyperostosis or acrodynia.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

1. Goodyear AW. Changing trends in clinical workup. *Bull Eur Pediatr* 2011;7:131–139.
2. Goodyear AW, Hall C. Expertise in clinical pediatrics. *Bull Eur Pediatr* 2015;11:32–37.

BOOKS/MONOGRAPHS

1. Gupte S. Differential Diagnosis in Pediatrics, 5th edn. New Delhi: Jaypee 2008.
2. Gill D, O' Brien N. Pediatric Clinical Examination, 5th edn. London: Churchill Livingstone 2007.
3. Stones E. Pediatric Check-up, 6th edn. London: Smith and Smith 2015.

DEFINITIONS

Growth, a measure of physical maturation, signifies an increase in size of the body and its various organs. Thus, it can be measured in terms of centimeters and kilograms.

Growth is mainly due to the multiplication of cells and increase in intracellular substance. Tissues show an increase in deoxyribonucleic acid (DNA) content. During the second half of pregnancy, an increase in cell size with increase in protein/DNA ratio occurs. Until 10 years of age, this increase is high, but thereafter it becomes slow. Unlike in the adult, growth is an essential feature of a child's life.

Development on the other hand is a measure of functional or physiological maturation and myelination of the nervous system. It signifies accomplishment of mental (acquisition of skills, etc.), emotional (development of attitudes, etc.) and social (adaptation to family and society, etc.) abilities. Unlike growth, it is rather difficult to assess development.

Though the terms **growth** and **development** are often used together, they represent two different aspects—**quantity** (growth) and **quality** (development). The two generally proceed concurrently. However, this may not always be so.

VARIOUS STAGES (PERIODS) OF GROWTH

Prenatal Stage

After the fertilization of the ovum by a sperm in the fallopian tube, the two-cell zygote develops. The zygote passes through the embryonic stage, in which the major body systems develop. Finally, after 8 weeks, it develops into the fetal stage, during which the baby's brain develops and the body adds size and weight. Figures 3.1 and 3.2 illustrate fetal developments.

- **Zygote:** 0–8 days after conception.
- **Embryo:** Until 8 weeks after conception. It differentiates into various structures and organs (organogenesis) of the body. When an embryo becomes a fetus at 8 weeks, it is approximately 3 centimeters in length from crown to rump and weighs about 3 g.
- **Fetus:** From 8 weeks up to birth. It is characterized by establishment of various vegetative functions. Prenatal development is most dramatic during the fetal stage. Although all of the organ systems are formed during embryonic development, they continue to develop

and grow during the fetal stage. By the time the fetus is considered full-term at 38 weeks gestation, it may be 50 cm long and 3.3 kg in weight (Box 3.1).

Postnatal Stage

- **Newborn:** First 28 days (4 weeks) of life. During this period, following the cutting of the umbilical cord, the baby establishes independent respiration and circulation and makes many more adjustments, such as feeding and weight gain.
- **Infancy:** First year of life.
- **Toddler:** 1–3 years; during this stage, the baby is able to walk, assume greater independence and participate in some family activities.
- **Pre-school (early childhood):** 3–6 years.
- **School-age (middle childhood):** 6–10 years for girls and 6–12 years for boys.
- **Pre-pubescent (late childhood):** 10–12 years in girls and 12–14 years in boys.
- **Pubescent:** 12–14 years in girls and 14–16 years in boys.
- **Post-pubescent:** 14–18 years in girls and 16–20 years in boys.

TYPES OF GROWTH STUDIES

Growth studies are of two types:

1. **Cross-sectional:** Here, each child in a large sample size is measured only once. It is less time consuming, economical and simple (i.e. easy to conduct). However, it fails to provide growth increment/decrement (velocity).
2. **Longitudinal:** Here, a group of children is followed from a particular age (say **birth**) to a particular point (say **maturity**). It is time-consuming, costly and somewhat difficult to undertake. Its major edge over cross-sectional study is that it provides the growth velocity and thereby the growth spurts.

The longitudinal study in which all participating subjects cannot be followed up over the full duration of study for logistic reasons is called **semi-longitudinal** or **mixed-longitudinal study**. The longitudinal study in which different observers undertake different parts of the study for a short time interval is called **linked-longitudinal study**.

VARIOUS FACTORS INFLUENCING GROWTH

The number of factors which influence growth are as mentioned below.

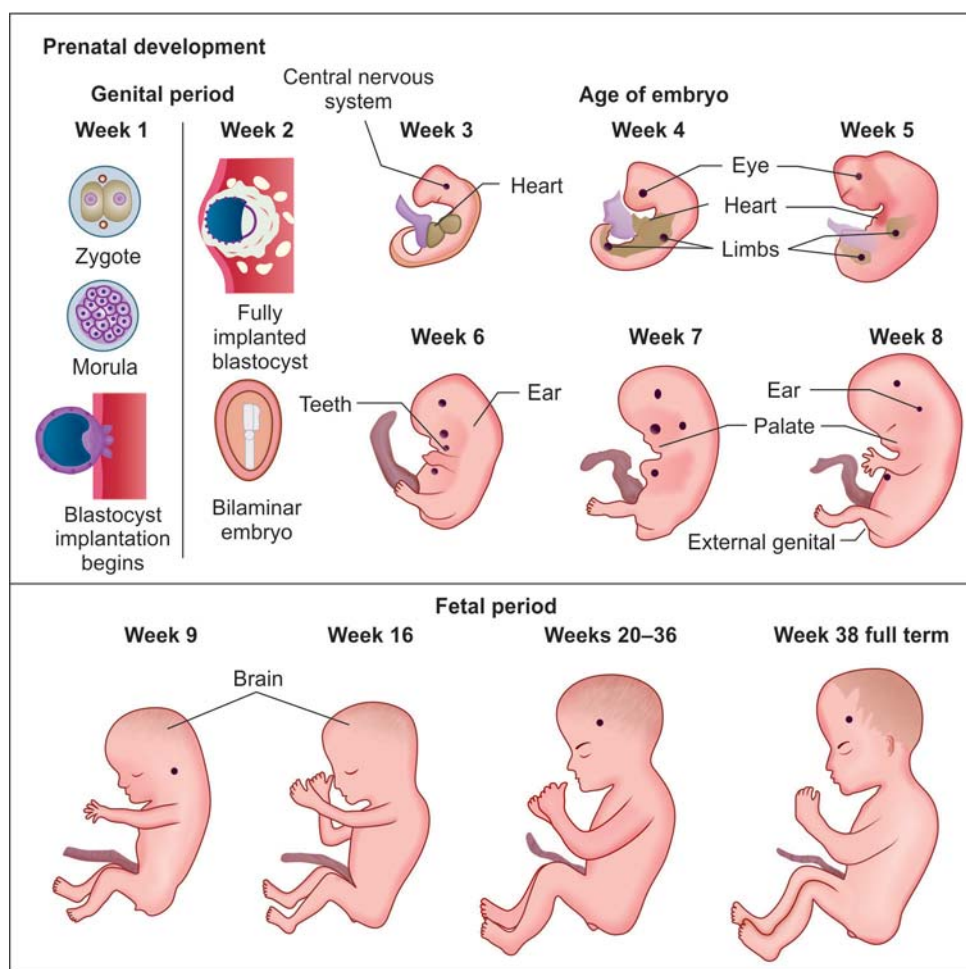


Fig. 3.1: Prenatal development. Prenatal development refers to the process in which a baby develops from a single cell after conception into an embryo and later a fetus.

Source: Encyclopedia of Children's Health. Available at: <http://www.healthofchildren.com/P/Prenatal-Development.html> Accessed on: 30 July 2015.

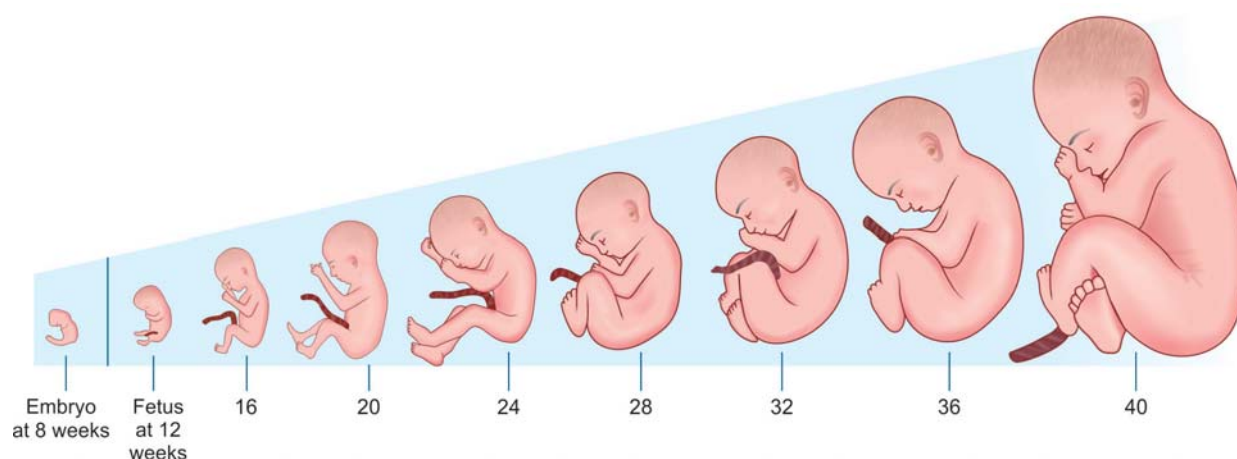


Fig. 3.2: Fetal growth from 8 weeks–40 weeks. All organ systems, though formed during embryonic stage, continue to develop and grow during the fetal stage.

Source: Encyclopedia of Children's Health. Available at: <http://www.healthofchildren.com/P/Prenatal-Development.html> Accessed on: 30 July 2015.

Genetic Factors

It is well known that certain hereditary influences may have a bearing on the ultimate constitution of the body.

- **Parental traits:** Tall parents are likely to have tall offsprings. Likewise, level of intelligence of parents influences the intelligence quotient (IQ) of their children.

- **Genetic disorders/abnormal genes:** Transmission of some abnormal genes may result in a familial illness, which affects the physical and/or functional maturation, e.g. phenylketonuria (PKU), thalassemia, hemophilia, mucopolysaccharidosis (MPS), galactosemia, etc. In addition, many inherited disorders, where bio-

Box 3.1**Landmarks in fetal development
(week-by-week)**

- **9–12 weeks:** The fetus measures approximately 8 cm in length; the head is approximately half the size of the fetus. External features such as the face, neck, eyelids, limbs, digits, and genitals are well formed. The beginnings of teeth appear, and red blood cells (RBCs) begin to be produced in the liver. The fetus is able to make a fist.
- **13–15 weeks:** The fetus reaches approximately 15 cm in length. Fine hair called **lanugo** first develops on the head; structures such as the lungs, sweat glands, muscles, and bones continue to develop. The fetus is able to swallow and make sucking motions.
- **16–20 weeks:** The fetus measures approximately 20 cm in length. Lanugo begins to cover all skin surfaces and fat begins to develop under the skin. Features such as finger and toenails, eyebrows, and eyelashes appear. The fetus becomes more active, and the mother can sometimes begin to feel fetal movements at this stage.
- **21–24 weeks:** The fetus measures approximately 28.5 cm in length and weighs approximately 0.7 kg. Hair grows longer on the head, and the eyebrows and eyelashes finish forming. The lungs continue to develop with the formation of air sac (alveoli); the eyes finish developing. It is at this stage that the startle reflex develops.
- **25–28 weeks:** The fetus measures approximately 38 cm in length and weighs approximately 1.2 kg. The next few weeks mark a period of rapid brain and nervous system development. The fetus gains greater control over movements such as opening and closing eyelids and certain body functions. The lungs have developed to allow air breathing.
- **29–32 weeks:** The fetus reaches approximately 38–43 cm in length and weighs approximately two kg. Fat deposits become more pronounced under the skin. The lungs remain immature, but breathing movements begin. The fetus's bones are developed, but not yet hardened.
- **33–36 weeks:** The fetus reaches approximately 41–48 cm in length and weighs 2.6–3.0 kg. Body fat continues to increase, lanugo begins to disappear, and fingernails are fully grown. The fetus has gained a high degree of control over body functions.
- **36–38 weeks:** The fetus reaches 48–53 cm in length is considered to be full-term by the end of this period. Lanugo has mostly disappeared and is replaced with thicker hair on the head. Fingernails have grown past the tips of the fingers. In a healthy fetus, all organ systems are functioning.

chemical defects are yet to be identified, are accompanied by the defect in growth and development.

- **Chromosomal disorders:** Many chromosomal disorders, including Down syndrome, Klinefelter syndrome, Turner syndrome, etc. are known to manifest in the form of growth and developmental aberrations.
- **Race:** Growth potential varies from race to race.
- **Sex:** Generally speaking, at birth, boys are taller and heavier than girls. When they mature towards adulthood, average height and weight of boys score over the girls.
- **Biorhythm:** Girls usually follow the same pattern of menarche and menstrual cycle as their mothers.
- **Twinning:** Multiple pregnancies usually result in small babies who are likely to attain low height and weight in the long run.

Intrauterine Factors

During intrauterine life, growth of the fetus depends on—fetal, placental and maternal factors.

Fetal Factors

- **Genetic potential:** Potential traits such as chest structure, fatty tissue, height, size of head and hands and feet.
- **Fetal hormones:** Thyroxine and insulin play a key role for adequate growth and development. Glucocorticoids come into play towards the end of gestation, influencing the prepartum maturation of liver, lungs, gut, etc. As yet, it is not clear if the growth hormone plays any role in fetal growth and development.
- **Fetal growth factors:** Several growth factors largely contribute to cell division and to some extent growth of tissues. Two types of fetal growth factors are:
 - **Growth promoting factors:** Insulin-like growth factor (IGF-1, IGF-2), epidermal growth factor (EGF), transforming growth factor (TGF-alpha), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), and nerve growth factor (NGF).
 - **Growth inhibitory factors:** Transforming growth factor (TGF-beta), Mullerian inhibitory substance, inhibin/activin family of proteins.

Placental Factors

Fetal weight and growth are influenced by placental weight and placental integrity of the placenta. With increasing fetal needs as the gestation progresses, placenta undergoes remodeling in structure and function (Box 3.2) as a part of adaptation.

Maternal Factors

Fetal health and size are influenced by maternal nutrition at conception and thereof as also mother's own fetal and childhood growth, acquired infections such as hepatitis B, human immunodeficiency virus (HIV), (T)oxoplasmosis, (O)ther agents, (R)ubella, (C)ytomegalovirus, and (H)erpes simplex (TORCH), (S)yphilis, (STORCH) and pre-existing maternal diseases (diabetes, heart disease, hypertension, chronic renal failure, hypothyroidism; antithyroid drugs administered for thyrotoxicosis).

To summarize, maternal-placental and fetal unit in most cases function in harmony in order to meet the requirements of the growing fetus (Box 3.2).

Box 3.2**Structural and functional changes in placenta during intrauterine life to meet the needs of growing fetus**

- Increase in villous surface area
- Decrease in diffusion distance
- Dilatation of fetal capillaries
- Decrease in fetoplacental vasculature resistance.

Postnatal Factors

During the postnatal period, genetic potentials and internal and external influences considerably influence the growth and development.

There is a significant overlap of factors during the fetal period and postnatal period, the former continuing the impact in the postnatal life. The following descriptions relates to both the periods.

Nutritional Factors

- Nutritional deficiency of proteins, calories, minerals, vitamins, and essential amino acids (especially lysine), both quantitative and qualitative, considerably retards physical growth. Also, other debilitating illnesses which interfere with adequate nutrition (say, malabsorption syndrome, tuberculosis, malignancy, chronic diarrhea/dysentery, intestinal parasitic infestations) exert the similar effect.
- **Maternal nutrition** before and during pregnancy has a profound effect on the growth of the fetus and the infant. Malnourished mothers, particularly if they continue to be fed poorly during pregnancy, are known to produce low birth weight (LBW) babies, especially with intrauterine growth retardation/restriction (IUGR). These small infants grow up into small adolescents/adults. In case of girls, they grow up to be small mothers who in turn give birth to LBW infants. This is termed as **intergenerational cycle of growth failure**. On the other hand, average birth weight of infants whose mothers are fed well during pregnancy is far higher.
- **Overnutrition** beyond a limit may cause obesity. Obesity, a major health hazard in the affluent countries, is now emerging in the developing countries too. Since undernutrition has failed to demonstrate a really significant downhill course, India suffers from dual burden of undernutrition on one hand and overweight and obesity on the other hand.
- **Undernutrition** affects the growth in weight far more than that of length/height. Nevertheless, chronic undernutrition spread over significant period leads to stunting (short stature). Figure 3.3 presents the intergenerational cycle of growth retardation/restriction.

Socioeconomic Factors

- **Poverty** is associated with diminished and affluence with good growth.

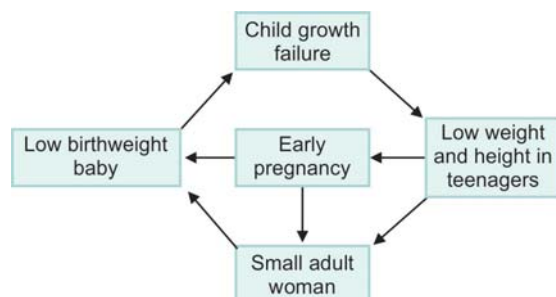


Fig. 3.3: Intergenerational cycle of growth retardation/restriction.

- **Socioeconomic status** has a bearing on growth. Children from well-to-do families with high socio-economic status usually evince better growth. Improved nutrition and living condition are known to contribute to better growth.
- **Parental education** affects child's growth. Children of well informed, educated parents, especially the mothers, are known to have superior growth.
- **Emotional factors** like lack of emotional support, anxiety, tension, etc. in parents (a common problem in broken families) adversely affect the release of growth hormone by the neurochemical regulation, resulting in poor growth of the child. On the other hand, children of parents who are well adjusted and happy have good growth.
- **Climate and weather** too have a bearing on child's growth. In summer, child's growth slows down, perhaps on account of factors such as enhanced incidence of infections and infestations. In spring, growth is better. It has also been observed that maximum weight gain occurs during fall and maximum height gain during the spring.
- **Cultural factors** such as beliefs, practices and traditions affect the growth of the child. Delay in initiating semisolids beyond 6 months of age, taboos against certain foods and use of prelacteal feeds in many communities have deleterious influence of child's growth.
- **Income and natural resources** influence child's growth via availability of improved nutrition and environments.

Environmental Factors

Physical surroundings (sunshine, hygiene, living standard) and psychological and social factors (relationship with family members, teachers, friends, etc.) affect growth and development.

Chronic Diseases

- Chronic diseases of the heart (congenital heart diseases, chronic rheumatic heart disease), chest (tuberculosis, asthma, and cystic fibrosis), kidneys (nephrotic syndrome, nephritis, and bladder neck obstruction), liver (cirrhosis, hydatid cyst), neoplasms, digestive or absorptive disorders, hypothyroidism, hypopituitarism, etc. impair growth.
- Metabolic disorders (glycogen-storage disease, renal acidosis) and mental retardation are associated with retarded growth.
- Adrenocortical overactivity causes excessive height in early childhood.
- High levels of growth hormone result in gigantism.
- Acute illnesses, in general, do not have any noteworthy effect on growth and development.

Growth Potentials

The smaller the child at birth (especially in context of gestation) the smaller she/he is likely to be in subsequent years. The larger the child at birth, the larger she/he is likely to

- 42 be in later years. Thus, the growth potential is somewhat indicated by child's size at birth.

Emotional Factors

Emotional trauma from unstable family, insecurity, sibling jealousy and rivalry, loss of parent(s), inadequate schooling, etc. all have negative effect on growth and development. Not infrequently, a plethora of unfavorable influences join hands to affect the growth and development adversely.

Hormonal Factors

- **Growth hormone:** The growth hormone is not needed for fetal growth, but its role in postnatal growth is significant.
- **Thyroxin deficiency:** Maternal hypothyroidism or maternal medication with antithyroid drugs and iodides in second half of pregnancy may cause fetal goiter and hypothyroidism with retardation of the skeletal growth of the fetus.
- **Insulin:** Diabetic mothers cause increase in fetal blood sugar that lead to hyperplasia of islets of Langerhans and elevation of insulin production. This results in stimulation of fetal growth. That is why fetus is large with high birth weight in diabetic mothers. Similar influence is exerted by a polypeptide produced by placenta (the so-called **IGF**).

POOR FETAL AND EARLY CHILDHOOD GROWTH AND ADULT DISEASE

Impaired growth of the fetus, newborn, infant and toddler has two major consequences in children who manage to survive:

1. **Stunting:** Chronic nutritional deprivation rather than causing wasting ends up in short stature as a compromise. India is known to harbor around 60–70 million stunted children i.e. more than one-third of the world's total population of stunted children.
2. **Adult life-style diseases:** According to Barker's hypothesis, origin of obesity, type 2 diabetes, hyperlipidemia, hypertension, coronary heart disease, etc. dates back to fetal life. These diseases develop in adult life as a consequence of programming. Also, See Chapter 1 (Pediatrics: Contemporary Trends).

PRINCIPLES OF GROWTH (LAWS OF GROWTH)

Order of Growth

Growth is a continuous as well as an orderly process. As a rule, human growth is cephalocaudal and distal-proximal. During intrauterine life, head (cephalic part), for instance, grows before neck, body and arms (caudal parts) and hands (distal part) grow before the arm (proximal part). During postnatal life, though growth of head becomes slow, extremities continue to grow fast. Head control occurs before the use of hands and creeping and crawling.

Growth occurs in a sigma fashion with periods of accelerated growth and slow growth. Fetal growth in first

half of gestation is much faster than in the second half. Postnatally, growth is accelerated in first few months of life and then at puberty.

Postnatal Growth Patterns

These are shown diagrammatically in Figure 3.4. As is evident, the general body growth is compared with genital, neural and lymphoid growth at various ages:

General (Somatic) Type

It pertains to body as a whole, external dimensions (with exclusion of head and neck), respiratory and digestive organs, aorta and pulmonary trunk, kidneys, spleen, blood volume and the whole of musculature and skeleton.

There are two periods of rapid general growth—**infancy** and **adolescence**. By around 18 years, 100% somatic growth is over.

Genital (Gonadal) Type

It pertains to testis, ovary, epididymis, uterine tube, prostate, prostatic urethra, and seminal vesicle. The genital growth is most rapid during early adolescence. As high as 90% is over by 13–15 years. In the preceding years, it is dormant and more or less a flat curve.

Neural Type

It pertains to brain and its parts, dura, many head dimensions, optic apparatus and spinal cord, etc. Neural growth is rapid during the latter months of intrauterine (fetal) life and early months of postnatal (neonatal) life. It continues fairly rapidly during the first few years of life and then gradually approaches the adult size. As much as 60% of total neural growth is achieved by two years and 90% by 3–6 years. The remaining 10% occurs in the rest of childhood and adolescence.

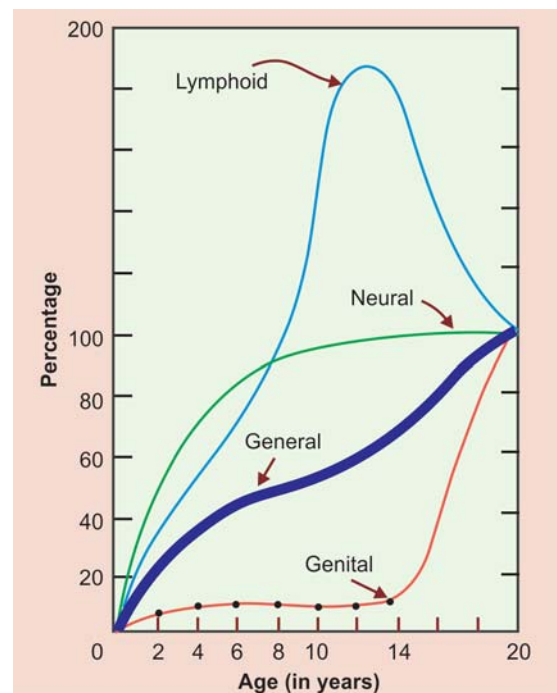


Fig. 3.4: Major types of postnatal growth curves.

Box 3.3 Rules of thumb about postnatal growth curves

1. **General body (somatic) growth** complete by 18 years.
2. **Neural growth** is 90% complete by 3–6 years
3. **Genital (gonadal) growth** is 90% complete by 13–15 years (early adolescence).
4. **Lymphoid growth** is 100% complete by 18 years. Around 7–8 years, it shoots beyond 100%, only to gradually regress to adult size by 18 years.

Brain growth is by and large faithfully reflected in the head size, i.e. occipitofrontal circumference (OFC), which at birth is around 35 cm or 65–70% of adult size. It grows rapidly in the first year, thereby gaining 12 cm so as to reach 47 cm size at one year. By two years, it is around 49 cm which comes to 90% of the adult size.

In a nutshell, intrauterine period and first two years (neonatal, infancy and second year) are critical for brain development. Development of neuromuscular function and cognition occurs in the subsequent years.

Lymphoid Type

It pertains to thymus, lymph glands and intestinal lymphoid masses. Lymphoid growth is rapid in infancy and highly accelerated in mid-childhood, shooting beyond 100% (more than adult size) around 6–8 years. It rapidly drops to the adult proportions during latter part of adolescence.

There is the clinical significance of this pattern of lymphoid growth. In mid-childhood, it is usual to find palpable lymph nodes in normal children. This need not be a matter of concern. Finally, it is important to reemphasize four important facts about postnatal growth curves (Box 3.3).

Variations in Body Proportions

At different ages, body growth is not uniform. As for instance, during infancy, head is much larger in relation to the size of the rest of the body. This proportion gradually changes to assume the adult ratio in the subsequent years of childhood and adolescence.

In younger children, the limbs are relatively short. The relationship of sitting height (trunk and head) with total height is a useful index in the diagnosis of certain disorders of growth. In a child with hypopituitary dwarfism, the body proportions correspond to chronological age. Body proportions in a child with hypothyroidism, on the other hand, are expected to be infantile.

Types of Body Build (Somatotypes)

According to Sheldon somatotype classification of human physique, the individuals can be categorized as ectomorphic, endomorphic or mesomorphic (Box 3.4).

Somatic Growth

It has two components—(1) **skeletal maturity** and (2) **eruption of teeth**.

Box 3.4 Sheldon's types of body build (physique)

- **Ectomorphic:** Relative preponderance of linearity, light bone structure, small musculature and subcutaneous tissue in relation to body length and large surface area.
- **Endomorphic:** Relative stocky build and large amount of soft tissue.
- **Mesomorphic:** Between the ectomorphic and endomorphic. Relative preponderance of muscle, bone and connective tissue with heavy, hard physique of rectangular outline.

Skeletal maturation is a continuous process, runs parallel to sexual maturation. It is only at the time of pubertal spurt that it accelerates. Else, it remains steady.

Assessment of skeletal maturation (bone age) is based on:

- Appearance and fusion of epiphyseal centers at the end of long bones in X-rays.
- Bone-mineral density in dual-energy X-ray absorptiometry (DXA).

There are 20 primary teeth, 10 each in upper and lower jaws. Lower central incisors are the first to erupt. Thereafter, upper jaw teeth erupt earlier than those in lower jaw, excepting second molar. Permanent teeth show first eruption at seven years with the appearance of first molar. More details about both bone age and teething are given later in this very chapter.

Growth spurts

Acceleration of growth is a characteristic of three periods (the so-called **growth spurts**):

1. First year (infantile growth spurt)
2. Six to eight years (mid-childhood growth spurt)
3. Adolescence (adolescent growth spurt)

IMPORTANT CRITERIA/INDICES FOR ASSESSMENT OF GROWTH

Growth, a remarkable feature of childhood is a continuous and dynamic process. It begins at conception and continues through infancy, childhood and adolescence until the child matures into an adult. Its assessment and monitoring are mandatory to detect any faltering and then take remedial measures.

Weight

On an average, ideal birth weight is around 3.25 kg. The newborn loses upto 10% of his weight during the first week. It is, however, regained by the age of 10 days. After this, weight gain occurs at a rate of 25–30 g a day for the first three months and 400 g a month during the rest of the first year of life. Thereafter, gain is two kg/year till the age of seven years followed by three kg/year till pubertal growth spurt appears.

The infant doubles his birth weight by the age of 4–6 months and trebles it by one year. He increases it four times by two years, five times by three years, six times by five years and ten times by ten years.

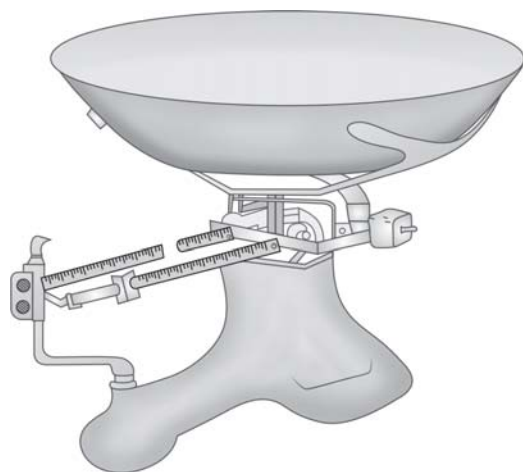


Fig. 3.5: Conventional beam balance. A conventional beam balance scale for weight recording of infants.



Fig. 3.6: Digital balance. A digital scale for weight recording of infants.

For convenience, you may remember:

Weight (kg) at birth = 3.25

Weight (kg) at 3–12 months = $\frac{\text{age (months)} + 9}{2}$

Weight (kg) at 1–6 years = $\text{age (years)} \times 2 + 8$

Weight (kg) at 7–12 years = $\frac{\text{age (months)} 7 - 5}{2}$

Ideally, a beam (lever) type (Fig. 3.5) or electronic type (Fig. 3.6) of weighing machine should be used in hospital and clinic practice to record infant's weight.

For field, an Indian modification of the famous English Salter spring machine (Fig. 3.7) is good enough, provided that its accuracy is checked periodically. It is a portable gadget, weighing only two kg, and is accurate upto 100 g. A scale that can record upto 20 kg is available. Thus, all under-five children can be weighed with the same machine. For weighing, the infant is suspended in a canvas or strong cloth holder while the machine itself is hung from a hook, a peg or the leg of an upturned string bed. Even an attendant can hold it up by hand till the weight is recorded. Time to time testing of its accuracy is vital.



Fig. 3.7: Hanging scale for weight recording in field practice.

Children who can comfortably stand can be weighed in a conventional weighing machine (Fig. 3.8) or, preferably a beam balance (Fig. 3.9) or electronic scale.

Length/Height

On an average, the ideal length of a full-term infant at birth is 50 cm. It rises to 60 cm at three months, 70 cm at nine months, 75 cm at one year, 90 cm at two years, 95 cm at three years and 100 cm at four years. Thereafter, the child gains little over 5 cm every year until 10 years. With the onset of puberty, remarkable acceleration in height gain occurs.

For convenience, you may remember:

Length (cm) at birth = 50

Length/height (cm) at one year = 75

Height (cm) at 2–12 years = $\text{age (years)} \times 6 + 77$

Half of the adult height is attained by two years in girls and 2½ years in boys.

Mid parental height (MPH) a good predictor of adult height is calculated by the following formula:

MPH in boys = $\frac{\text{Father height's} + \text{Mother's height} + 13}{2}$

MPH in girls = $\frac{\text{Father height's} + \text{Mother's height} - 13}{2}$

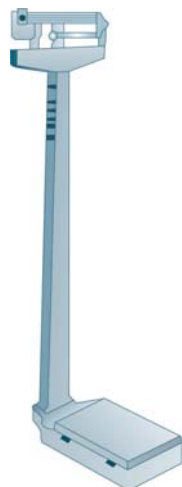


Fig. 3.8: Beam balance. A beam balance or electronic scale is a better option for weighing toddlers, older children and adolescents.



Fig. 3.9: Electronic scale. Toddlers and older children and adolescents can be weighed on conventional weighing machine.

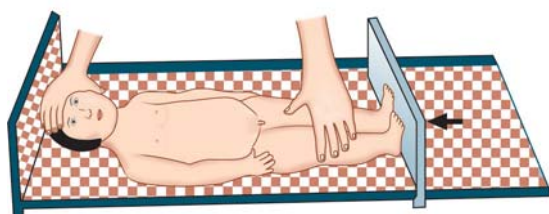


Fig. 3.10: Infantometer for recording recumbent length. In case this kind of an infantometer is not readily available, the purpose is served with a fabricated infantometer employing a book at the head-end and another at the foot-end of the infant (in lying down posture). Proper alignment of head and feet and straightening of legs is important for accuracy.

For children under two years, it is advisable to measure the recumbent length, while the child lies supine, (with legs fully extended at hips and knees and feet at right angles to legs) in the so-called *infantometer* (Fig. 3.10). Such an infantometer may be fabricated by placing a book vertically at the head-end and another at the foot-end.

In older children, **standing height** is measured by making the child stand against a vertical scale fixed on a stand (*stadiometer*) as shown in (Fig. 3.11) or simply against a wall and then marking the highest point of the vertex on the wall, using the head piece or simply a book. Make sure that the child stands comfortably with heels, buttocks, shoulders and back of the head touching the wall and the feet parallel. Arms should hang naturally by the sides. The line joining the upper margin of the external auditory meatus and lower margin of the orbits (Frankfort horizontal plane) should be in the plane parallel to the floor. Good quality steel measuring tape rather than that of a tailor should be employed. The height should be recorded to the nearest 0.1 centimeter. Now, digital ultrasonic height measuring system too has become available.

Weight for Height

It is calculated by dividing actual weight by expected weight corresponding to the height and then multiplying the quotient by 100. A value below 90.5% indicates malnutrition and above 120% overweight/obesity.



Fig. 3.11: Stadiometer for height. The child stands erect, barefooted, feet flat on ground. It should be ensured that the head (occiput), shoulders, buttocks and heels are touching the vertical background. The sight should be parallel to the ground (Frankfort plane).

Growth Velocity

Growth velocity (GV) is the rate at which the child grows over a period of time. Beyond the neonatal and infancy period, rather than weight, it is the height that is more useful as an indicator of growth, especially when two measurements are recorded at an interval of about six months. Growth velocity oscillates around 50th centile.

For determining GV (in other words, height velocity), height needs to be measured on more than one occasion over a period of time and the increment in height divided by the lapse of time in between.

The formula for growth velocity (GV):

$$GV \text{ (cm)} = \frac{\text{Present height (cm)} - \text{Initial height (cm)}}{\text{Time period between two measurements (years)}}$$

contd...

Growth velocity index (GVI) is provided as:

$$GVI = \frac{\text{Actual GV}}{\text{Expected growth velocity for chronologic age}} \times 100$$

Standard on score (SDS) is given as:

$$SDS = \frac{\text{Height (cm)} - \text{height (cm) at 50th percentile for age}}{\text{Standard deviation (SD) of height for age (cm)}}$$

Table 3.1: Upper segment/lower segment ratio at various ages

Various ages	Upper/lower segment
Birth	1.7: 1
6 months	1.6: 1
1 year	1.5: 1
2 years	1.4: 1
3 years	1.3: 1
4 years	1.2: 1
5 years	1.1: 1
7 years	1: 1
Adolescence	0.9: 1

Body Ratios/Proportions

- **Upper/lower segments ratio** (as measured from the pubis symphysis) at birth is 1.7:1. With the greater increase in the length of the legs compared to the trunk, the ratio is 1.6 at six months, 1.5 at one year, 1.4 at two years, 1.3:1 at three years; after seven years and, usually by the age of 10–12 years, the ratio becomes approximately 1:1. Thereafter, lower segment tends to show a slight edge over the upper segment, the ratio being 0.9:1 by adulthood (Table 3.1).
- **Stem stature index** refers to the sitting height (crown-rump length) as a percentage of the total height or recumbent length. It is 70 at birth, 66 at six months, 64 at one year, 61 at two years, 58 at three years, 55 at five years and 52 at puberty {sexual maturity rating (SMR)-3 for girls, SMR-4 for boys}.
- **Span** is the distance between tips of middle fingers when the arms are outstretched. It is equal to height at 10 years. In earlier years, it is 1–2 cm less than the length/height. After 12 years, it is 1–2 cm more than height.

Head Circumference

- **Size:** It is also called **occipitofrontal circumference (OFC)**, head circumference, which represents growth of the brain, measures 34–35 cm at birth, 41 cm at three months, 44 cm at six months, 47 cm at one year, 50 cm at three years, 51 cm at seven years, 52 cm at 12 years and 53 cm at 14 years (Table 3.2).

For measuring head size, cross-tape method is employed. The tape (non-stretchable) is placed over the occiput at the back and just above the supraorbital ridges in front (mid forehead). The point of highest circumference is measured (Fig. 3.12).

Generally speaking, if brain does not develop normally, as in intellectual disability (mental retardation), the head size is likely to be small (Fig. 3.13). Occasionally, however, the small size of the head may be secondary to premature union of the skull sutures; the so-called **craniosynostosis** (also termed **craniostenosis**).

Large head may be the result of hydrocephalus, rickets, chondrodystrophy or syphilis. It may even be familial macrocephaly which is just harmless.

- **Shape:** A boat-shaped head denotes scaphocephaly, asymmetrical head the plagiocephaly and tower shaped head the oxycephaly or acrocephaly. Flattened occiput may be a feature of Down syndrome whereas frontal and/or parietal bossing or box-like head is suggestive of rickets.
- **Fontanels and sutures:** At birth, there are six fontanels, one each anterior and posterior (Fig. 3.14) and four lateral (two anterolateral and two posterolateral). Posterior and lateral fontanels close fairly early—usually within first few weeks.
- Anterior fontanel (AF) which is of much clinical value is rhomboid (diamond)-shaped and measures 3 × 2 cm

Table 3.2: Head circumference at different ages in healthy children

Various ages	Head circumference (cm)
Birth	35
3 months	41
6 months	44
12 months	47
3 years	50
7 year	51
12 year	52
14 year	53



Fig. 3.12: Measurement of head circumference. Occipitofrontal circumference employing cross-tape method.

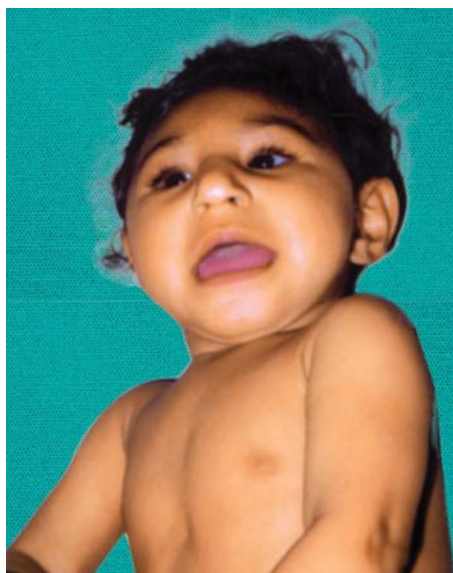


Fig. 3.13: Microcephaly. This 1-year-old had head circumference of 41 cm (against a normal of 47 cm), global developmental delay and multiple congenital deformities.

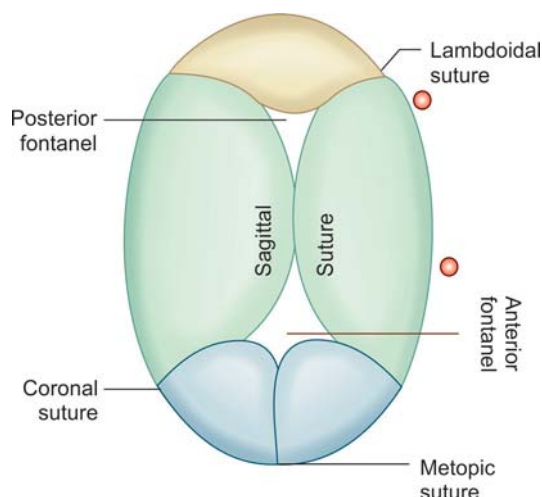


Fig. 3.14: Fontanels and sutures. Skull top, showing fontanels and sutures.

opposite angles and 2.5×2.5 cm midpoints of opposite sides. In most cases, it closes between 9 months and 18 months.

- **Early closure** of AF may suggest craniosynostosis or primary microcephaly.
- **Late closure** should arouse suspicion of rickets, congenital hypothyroidism, hydrocephalus, syphilis, protein-energy malnutrition, etc. Rare causes include achondroplasia, Apert syndrome, cleidocranial dysostosis, hypophosphatemia, rubella, prematurity, IUGR, osteogenesis imperfecta, trisomies and hypopituitarism.
- Occasionally, AF patency may be familial.

CHEST CIRCUMFERENCE

For measuring chest circumference place the tape at the level of the nipples (or xiphisternum) in a plane at right angle to the spine. Record the measurement in mid res-

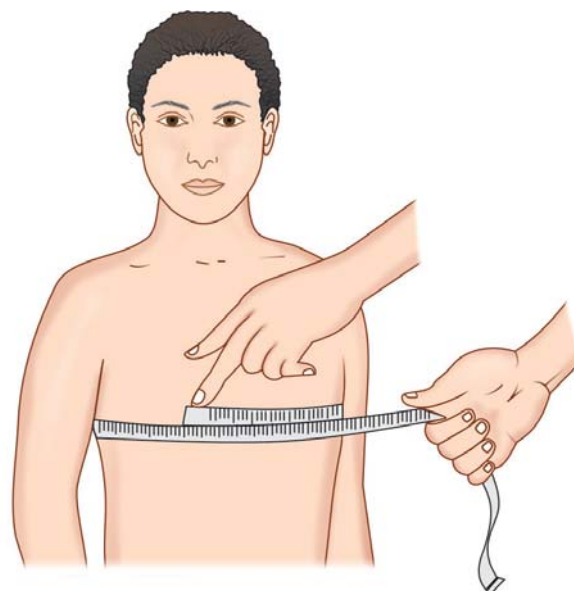


Fig. 3.15: Chest circumference. Measurement of chest circumference at the level of the nipples.

piration, i.e. midway between inspiration and expiration to the nearest 0.1 cm (Fig. 3.15 and Table 3.3). Also, See Chapter 12 (Infant and Young Child Feeding).

Head/Chest Circumference Ratio

At birth, head circumference is larger than chest circumference by about 2.5 cm. By 6–12 months, both are equal. After first year, chest circumference tends to be larger by 2.5 cm. By the age of five years, it is more or less 5 cm greater in size than the head circumference.

Mid Upper-arm Circumference

Let the left arm hang naturally by the side of body. Then place the tape firmly, but without compressing the tissues around the upper arm at a point midway between tip of the acromion and olecranon process (Figs 3.16 and 3.17, Box 3.5 and Table 3.4).

In preschool children (1–5 year) measurement less than 11.5 cm means severe malnutrition, 11.5–12.5 cm moderate malnutrition and 12.5–13.5 cm mild malnutrition. Also, See Chapter 13 (Malnutrition).

Skin-fold Thickness

Of the various skin-folds (subscapular, biceps and triceps), triceps skin-fold is the most widely employed in children. It is measured by a specialized instrument called **skin-fold calipers**. Two most dependable are—**Herpenden's** (Fig. 3.18) and **Lange's skin-fold calipers**.

The measurement is usually done at the mid upper-arm over triceps area on the left side (triceps skin-fold thickness). A fold of skin is held between the thumb and index finger and measured.

Ratio of total body water and body weight is a more accurate index of body fat, correlating at about 0.62 with skin-fold thickness (Table 3.5).

Table 3.3: Chest circumference (cm) of children under six years

Age in months	Harvard standard	Percentage of the reference									
		95	90	85	80	75	70	65	60	55	50
3	40.6	38.5	36.5	34.5	32.5	30.5	28.4	26.4	24.4	22.1	20.3
6	43.1	41.5	39.2	37.0	34.9	32.7	30.6	28.4	26.2	24.0	21.9
9	46.0	43.7	41.4	39.1	36.8	34.5	32.2	29.9	27.6	25.3	23.0
12	47.3	44.9	42.6	40.2	37.8	35.5	33.1	30.7	28.4	26.0	23.6
15	48.3	45.9	43.5	41.0	38.6	36.2	33.8	31.4	29.9	26.5	24.1
18	49.2	46.7	44.3	41.8	39.4	36.9	34.4	32.0	29.5	27.1	24.6
24	50.4	47.9	45.4	42.8	40.3	37.6	35.3	32.8	30.2	27.7	25.2
30	51.5	48.9	46.3	43.8	41.2	38.6	36.1	33.5	30.9	28.3	25.7
36	52.2	49.6	47.0	44.4	41.8	39.2	36.6	34.0	31.3	28.7	26.1
42	52.3	50.2	47.5	44.9	42.2	39.6	37.0	34.3	31.7	29.0	26.4
48	53.4	50.7	48.1	45.4	42.7	40.0	37.4	34.7	32.9	29.4	26.7
54	54.0	51.3	48.6	45.9	43.2	40.5	37.8	35.1	32.4	29.7	27.0
60	54.6	51.9	49.1	46.4	43.7	41.0	38.2	35.5	32.8	30.0	27.3
Boys 66	55.3	52.5	49.8	47.0	44.2	41.5	38.7	35.9	33.2	30.4	27.6
72	56.1	53.3	50.5	47.7	44.9	42.1	39.3	36.5	33.7	30.8	28.0
Girls 66	53.7	51.0	48.3	45.6	43.0	40.3	37.6	34.9	32.2	29.5	26.8
72	54.5	51.8	49.0	46.3	43.6	40.9	38.1	35.4	32.7	29.9	27.2

**Fig. 3.16:** A–Z of mid upper-arm circumference measurement using Shakir's tape.

Body Mass Index

Body mass index (BMI) correlates well with the subcutaneous fat and the total body fat and, yet allows a variation in the lean body mass.

It is calculated by the following formula:

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2} = \text{kg/m}^2$$

BMI remains constant upto the age of five years. A BMI >25 kg/m² points to overweight and >30 kg/m² establishes existence of obesity.

In pediatric practice:

- BMI of 22–25 kg/m² suggests overweight
- BMI >25 obesity

- BMI <15 kg/m² points to significant malnutrition:

- 15–18.5—mild
- 13–15—moderate
- <13—severe

Bone Age

Bone age implies to age as calculated from the maturation and appearance of epiphyses.

An average full-term newborn has five radiologically demonstrable ossification centers (Box 3.6).

At birth, there is no calcification in the carpal bones. Ossification of the carpal bones occurs in a predictable sequence, starting with the capitate and ending with the pisiform (Figs 3.19 and 3.20).

By the age of six months, ossification centers for two carpal bones, i.e. capitate and hamate, appear. It is a useful guide to remember that number of centers at wrist is equal to age in years plus one. Thus, a child of two years should have three centers in an X-ray of wrist.

Although there is a great individual variability, approximate ossification time frame lines are as given in Box 3.7.

Table 3.6 gives the recommended sites for bone age determination radiologically.

Epiphyseal development of girls is consistently ahead of the boys. Box 3.8 lists the causes of advanced and retarded bone age.

Usually epiphyseal (supernumerary centers, pseudoepiphysis and notches) and sometimes non-epiphyseal anomalies may well indicate pathologic states such as malnutrition, encephalopathies, endocrinopathies. Down syndrome or congenital and familial structural defects.

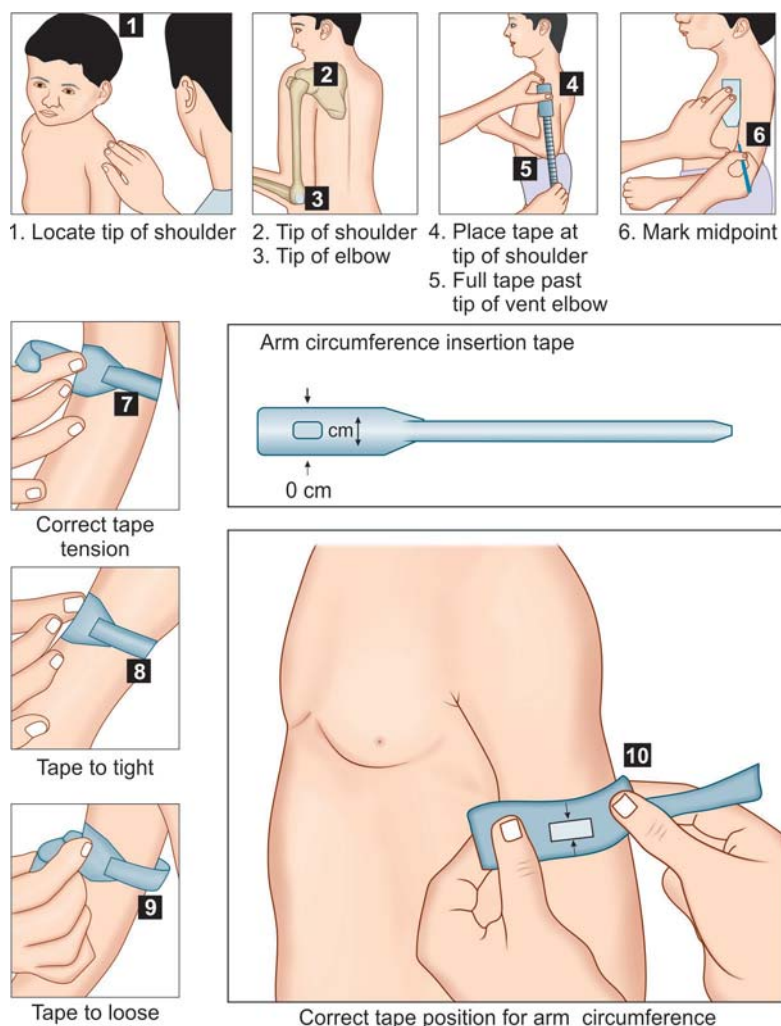


Fig. 3.17: Measurement of mid-upper arm circumference. Note that the level at which measurement is recorded lies at the center of a line between tip of acromion and olecranon process of ulna. The currently recommended MUAC tape (modified Shakir's tape) is provided with green zone (>13.5 cm, normal), yellow zone (11.5–13.5 cm, mild-moderate malnutrition) and red zone (<11.5 cm, severe malnutrition).

Box 3.5 Steps of mid-upper arm circumference measurement

- Ask the mother to remove any clothing that covers the child's arm. If possible the child should stand erect and sideways to the measurer.
- Estimate the mid-point of the left arm (between tip of the acromion process and olecranon process of ulna).
- Straighten the child's arm and wrap the tape around at the mid-point. Make sure that the numbers are right side up. Make sure the tape is flat around the skin.
- Inspect the tension of the tape on the child's arm. Make sure the tape has the proper tension and is not too tight or too loose. Repeat any step as necessary.
- When the tape is in the correct position and correct tension on the arm, read and call out the measurement to the nearest 0.1 cm.
- Immediately record the measurement.

Dentition

It is not a dependable parameter for assessment of growth since there is a wide variation in the eruption of teeth and its timing.

The average age at which first tooth erupts is 6–7 months. The rest of the milk, deciduous or temporary

teeth appear at the rate of one tooth every month. Thus, the number of teeth in an infant age—age in months minus 6. By 2½ to 3 years, the child has a full set of temporary teeth numbering 20.

Generally, the lower central and lateral incisors erupt earlier followed by first molars, cuspids and second molars in succession.

Rarely, a baby may be born with an already erupted tooth (natal tooth). It is harmless as long as it is not loose and does not interfere with feeding.

Delayed Eruption

Delayed eruption of first tooth (upto as late as 15 months) in a normal child is also seen. Likewise, late appearance of other teeth may also be there. Among the possible factors responsible for delayed dentition include:

- Familial and/or racial tendency,
- Poor nutritional status,
- Rickets,
- Osteogenesis imperfecta.

Very infrequently, a child may have an absolute non-eruption of teeth (anodontid) which is a classical feature of ectodermal dysplasia.

Table 3.4: Arm circumference (cm) of children under six years

Age in months	Polanski standard	Percentage of the reference								
		95	90	85	80	75	70	65	60	55
Boys 5	12.1	12.1	11.4	10.8	10.2	10.6	8.9	8.2	7.6	7.0
6	14.5	13.8	13.1	12.4	11.6	10.9	10.2	9.4	8.7	8.0
9	15.8	15.0	14.2	13.4	12.6	18.1	11.0	10.2	9.5	8.7
12	16.0	15.2	14.4	13.6	12.8	12.0	11.2	10.4	9.6	8.8
15	16.1	15.3	14.5	13.7	12.9	12.1	11.3	10.5	9.7	8.8
18	15.7	14.9	14.1	13.3	12.5	11.9	11.0	10.3	9.4	8.6
21	16.2	15.4	14.6	13.7	13.0	12.1	11.4	10.5	9.7	8.9
24	16.3	15.5	14.7	13.8	13.3	12.2	11.4	10.6	9.8	8.9
30	16.4	15.6	14.8	13.9	13.1	12.3	11.5	10.7	9.9	9.0
36	16.2	15.4	14.6	13.7	13.0	12.1	11.3	10.5	9.7	8.9
42	16.5	15.7	15.0	14.0	13.2	12.4	11.6	10.7	9.9	9.1
48	16.9	16.0	15.2	14.4	13.5	12.7	11.8	11.0	10.1	9.3
54	17.5	16.6	15.5	14.9	13.8	13.1	12.1	11.4	10.4	9.6
60	17.0	16.1	15.3	14.5	13.6	12.8	11.9	11.1	10.1	9.4
Girls 3	13.3	2.7	12.0	11.3	10.6	9.9	9.3	8.9	8.0	7.3
6	14.3	3.6	12.9	12.2	11.5	10.7	10.0	9.3	8.6	7.9
9	15.3	14.5	13.7	12.9	12.2	11.7	11.4	9.9	9.2	8.4
12	15.6	14.8	14.0	13.3	12.5	11.7	10.9	11.7	9.4	10.1
15	15.7	14.9	14.1	13.3	12.5	11.9	11.0	10.3	9.4	8.6
18	16.1	15.3	14.5	13.7	12.9	12.1	11.3	10.5	9.7	8.8
21	15.9	15.1	14.3	12.5	12.7	11.9	11.1	10.3	9.6	8.7
24	15.9	15.1	14.4	12.5	12.8	11.9	11.2	10.3	9.6	8.7
30	16.4	15.6	14.8	13.9	13.1	12.3	11.5	10.7	9.8	9.0
36	15.9	15.1	14.3	12.5	12.7	11.9	11.1	10.3	9.6	8.7
42	16.3	15.5	14.7	13.8	13.1	12.2	11.4	10.6	9.8	8.9
48	16.9	16.0	15.2	14.8	13.5	13.7	11.8	11.0	10.2	9.3
54	16.6	15.8	15.1	14.1	13.4	12.4	11.7	10.8	10.1	9.1
60	16.9	16.0	15.2	14.3	13.5	13.7	11.8	11.0	10.1	9.3
72	17.3	16.4	15.6	14.7	13.8	13.0	12.1	11.2	10.4	9.5



Fig. 3.18: Herpenden's skin-fold caliper. This is the most dependable and accurate caliper for measuring skin-fold thickness. The caliper is designed to exert a constant pressure of 10g/mm. Each division on the scale is 0.2 mm. It is expensive, costing around US \$ 350–400.

Discoloration of temporary teeth right from the start may well be related to ingestion of outdated tetracycline's by the mother during the third trimester of pregnancy.

Table 3.5: Skin-fold and mid upper-arm circumference

Age	Biceps skin-fold (mm)		Triceps skin-fold (mm)		Mid upper-arm circumference (cm)	
	Male	Female	Male	Female	Male	Female
Birth	—	—	4.8	5.0	12.2	12.0
1 Year	6.5	6.6	10.0	9.6	12.6	12.5
3 Years	5.8	6.2	9.5	9.9	13.6	13.3
6 Years	4.6	5.6	7.9	8.2	14.9	14.8
9 Years	4.1	4.2	7.4	7.8	16.5	16.5
12 Years	4.2	4.2	8.0	8.1	17.4	18.2
15 Years	3.8	3.8	7.3	7.4	20.3	20.6

There is no truth in the commonly held belief that teething causes diarrhea or fever. However, teething may be responsible for excessive salivation and drooling, irritability, painful gums and disturbed sleep. Local application of choline salicylate and an oral analgesic or a mild sedative should suffice.

The first permanent teeth—the six year molars are sometimes confused with the temporary teeth.

Box 3.6**Five radiologically demonstrable ossification centers present at birth**

1. Distal end of femur
2. Proximal end of tibia
3. Talus
4. Calcaneus
5. Cuboid.



Fig. 3.19: X-ray of hand and wrist. Between 1 and 12 years of age, radiograph of hand and wrist is most often employed for determination of bone age. Note the eight carpal bones.



Fig. 3.20: X-ray of wrist and hand: Note two carpal bones which as supposed to appear by six months and ossification center for radius which is supposed to appear around one year. Hence bone age is one year. Ossification center for distal end of ulna appears around five years.

Tables 3.7 and 3.8 summarize the pattern of the eruption of temporary and permanent teeth. The number of temporary and permanent teeth is shown in Table 3.9.

Physiological and Structural Growth

Salient features of growth of systems, organs and tissues should also be taken into consideration For instance:

Box 3.7**Time frame of appearance of ossification centers of carpal bones**

- Capitate: 1–3 months
- Hamate: 2–4 months
- Triquetrum: 2–3 years
- Lunate: 2–4 years
- Scaphoid: 4–6 years
- Trapezium: 4–6 years
- Trapezoid: 4–6 years
- Pisiform: 8–12 years

Table 3.6: Recommended sites (for X-ray) for bone age determination

Age	Site
Newborn	Foot and ankle
3–9 months	Shoulder
1–12 years	Hands and wrists
12–14 years	Elbow and hip

Box 3.8**Causes of abnormal bone age****Advanced bone age**

- Thyrotoxicosis
- Adrenal hyperplasia
- Precocious puberty
- Gigantism
- Pseudohypoparathyroidism
- Acrodysotosis
- Leprechaunism
- Syndrome of accelerated skeletal maturation and relative failure to thrive
- Rheumatoid arthritis and arteriovenous malformation of a limb (only the affected bone(s) may show an advanced bone age)

Retarded (delayed) bone age

- Congenital hypothyroidism
- Growth hormone deficiency
- Constitutional short stature
- Turner's and Noonan's syndromes.

- Lymphoid tissue shows enormous growth, going much beyond the adult size during early adolescence. Eventually, it shows regression, settling to adult size.
- Respiratory rate shows a sharp fall during first two years. Thereafter, the decrease is slow throughout childhood.
- Pulse rate behaves on the same lines as respiratory rate.
- Blood pressure shows a steady rise after 6 years of age.
- Among the paranasal sinuses, ethmoid, maxillary and sphenoid sinuses are present at birth.
 - **Ethmoid sinuses** attain their optimal size by 7–14 year; others do so during puberty only.
 - **Frontal sinus** is radiologically visible around 6 year of age.

GROWTH CHART**(Road to Health Chart)**

The brain-child of Prof. David Morley, growth chart is defined as a visible display of child's growth and development.

Table 3.7: Temporary (primary) teething/dentition

Age	Eruption
Birth	Nil
6–7 months	Central incisors
By 10 months	Laterals incisors
1–1½ years	First molars
1¼–1¾ years	Cuspids (Canines)
2–3 years	Second molars

Table 3.8: Permanent (secondary) teething/dentition

Age	Eruption
6 years	First molars
8 years	Central and lateral incisors
9 years	Bicuspid (anterior)
10 years	Bicuspid (posterior)
11–12 years	Canines
12–13 years	Second molars
17–25 years	Third molars (wisdom teeth)

Table 3.9: Number of teeth

Temporary	edcbaabcde	20
	edcbaabcde	
Permanent	87654321 12345678	32
	87654321 12345678	

Goal

Its goal is to have serial record of child's weight periodically on a growth chart which is based on percentile curves. A flat curve indicates a slowed or arrested growth which must alert the attending doctor to take action, both diagnostic as to its cause and corrective so as to lead to normal growth once again.

Types

- **WHO growth chart** has the upper reference curve representing the 50th percentile (for boys) and the lower curve the 3rd percentile for girls. The new WHO growth charts use 2006–2007 WHO growth standards rather than the National Center Health Statistics (NCHS) standards which had been in use since 1970s.
- **Government of India growth chart**, as modified in 2009, has four curves; the topmost representing 80% (50th percentile), followed by 70%, 60% and 50% of the median of the 2006–2007 WHO standards. Correspondingly mild, moderate and severe malnutrition can be detected.
- **Mother and child protection card** provides space for family identification and registration, birth record, pregnancy record, details about immunization, milestones, breastfeeding, introduction of complementary foods, etc.
- **Integrated child development services (ICDS) growth chart** has over and above the standard, 3 reference lines.

- **Indian academy of pediatrics (IAP) growth chart** incorporates immunization, development and health records as well.

Applications (Uses)

The chart is meant:

- To make growth a tangible visible attribute.
- To create a felt need, a demand for growth.
- To detect the earliest signs of faltering growth.
- To reinforce effective behavior resulting in optimal growth.
- To illustrate the adverse effects of various negative events or circumstances on growth (infection, maternal deprivation, seasonal scarcity, etc)
- To facilitate the transfer of information to the mother regarding means to promote growth.
- To teach about the importance of proper infant and young child feeding and adverse effects of measles, diarrhea or pneumonia.

The growth chart is primarily meant for the mother to visualize and motivate concern for healthy growth in her child. It should, therefore, be sufficiently attractive and designed to facilitate accurate recording in a simple manner and enable mothers to recognize growth faltering at the earliest stage.

GROWTH MONITORING

Definition

Growth monitoring and promotion (GMP) is an operational strategy of regular and sequential measurements for the assessment of growth and development of the child in the community in order to promote optimal health.

Features

- The strategy recognizes growth to be the result of overall health, nutrition, environment, social, psychic and developmental factors rather than sheer nutrition.
- It involves mothers and health workers in a meaningful and reinforcing way, aiming at the action before overt malnutrition occurs.
- As far as possible, it should be a mother-to-mother strategy facilitated and assisted by the health workers.
- Growth monitoring is best initiated from birth rather than when the child is already 2–3 years old.
- Growth monitoring is carried out by two methods:
 1. Growth chart use as described above.
 2. Alternative indicators:
 - Age-dependent—Height-for-age,
 - Age-independent—Weight-for-height, mid-upper-arm circumference.

Criticism

Doubts have been raised about the successful implementation of the GM programs. Perhaps, the deficiency lies in modus operandi in execution rather than an inherent deficiency in the strategy.

Table 3.10: Schedule of growth monitoring

Age group	Specific components of monitoring	Schedule
Birth–15 months	Length, weight, head circumference	6 weeks, 14 weeks, 6 months, 9 months, 15 months
18 month–3 years	Length, weight, head circumference	Every 6 months
3.5–5.5 years	Height, weight	Every 6 months
6–8 years	Height, weight + BMI	Every 6 months BMI yearly
9–18 years	Height, weight, BMI + SMR	Yearly

Abbreviations: BMI, body mass index; SMR, sexual maturity rating.

Schedule

Broadly, growth monitoring may be carried out in the schedule given in Table 3.10.

LINEAR CATCH-UP GROWTH

Monitoring linear catch-up growth is of great clinical importance because of its value in measuring the efficacy of therapy in impaired growth.

Definition

It is defined as height velocity above statistical limits of normal (supranormal) for age and/or maturity during a defined period of time following a transient period of growth inhibition.

- It is intended to revert the child to his pre-retardation growth curve. It is the rapid growth targeted at making up for the loss of potential tissue.
- It is not the same as compensatory growth. The latter is the growth that occurs after a loss of the actual mass of tissue that is controlled by a simple feedback mechanism working on physiological mass. An illustrative example is that of the liver regeneration following its partial resection.
- In quite a proportion of cases, it is possible to foresee the extent of likely catch-up growth. As for instance, short periods of growth arrest at a young age with prompt elimination of inhibitory factors and institu-

tion of suitable therapy usually leads to attainment of 53 full catch-up and potential target height. Nevertheless, catch-up growth is likely to be significantly less in case of recurrent episodes of growth inhibitory factors.

Influencing Factors

Principle factors influencing it includes:

- Nature, intensity and duration of the causative growth disorder responsible for retardation in height.
- Stage of initiation, type, duration, effectiveness and magnitude of nutritional therapy.
- Stage of growth of the child.

Types

Three types of catch-up growth are shown in Box 3.9.

Operative Factors

Two important factors, namely growth hormone and IGF-1 play vital role in linear growth, which is indeed the result of recruitment of new progenitor cells from the stem layer and the number of cell divisions in the hypertrophic layer. Obviously, the hormonal factors (especially the somatotrophic axis) and the epiphyseal growth plate are of paramount importance in catch-up growth.

Modus Operandi

The exact modus operandi of regulation of catch-up growth remains unclear. The three available hypotheses are given in Box 3.10.

GROWTH (REFERENCE) STANDARDS: LOCAL OR INTERNATIONAL?

The question whether the developing countries should use international growth standards or develop their own standards for comparison has been considerably debated.

- The argument that all children have same genetic potential/especially in early years, and their growth is more influenced by nutrition, illness, and environment rather than by heredity, and that growth of children of affluent groups in developing countries compares favorably with that of children in the developed countries had led WHO recommend the use of data collected from North American children as the single International reference standard to replace the earlier Harvard data. These data were popularly referred to as 1977 NCHS data.

Box 3.9 Features of three types of catch-up growth

- **Type 1:** It occurs in infancy and childhood. Once the cause for retardation is removed (say gluten-free diet in celiac disease), height velocity may shoot up as much as 4 times the normal for the chronological age. The height deficit is, therefore, rapidly eliminated.
- **Type 2:** It occurs in adolescence. Once the cause for retardation is removed, growth continues for longer than usual to compensate for the growth arrest, but there is either little or no increase in height velocity compared to the mean for chronological age.
- **Type 3:** It is a mixture of type 1 and 2. Here, once growth restriction stops an increase in height velocity and a delay and prolongation of growth occurs.

Box 3.10 Hypotheses for regulation of catch-up growth

- **Tanner's time tally/neuroendocrine hypothesis:** Catch-up stimulus is provided by a balance of several hormones released or coordinated by pituitary.
- **Growth plate hypothesis:** Catch-up growth is intrinsic to the growth plate and not to the central nervous system.
- **William's cellular hypothesis:** There is no single mechanism that regulates catch-up growth. Growth is a cellular phenomenon in which cell has a program and a mechanism to recognize its placement in the program. A dynamic stabilizing mechanism tends to bring it back to the right course in case it goes astray. The growth hormone coordinates the tissues and the organs at the program level.

- 54 ■ Following further revision in 2000, Center for Disease Control and prevention (CDC) growth charts and CDC growth tables remained in use.
- More recently, in 2006, based on data on breastfed children, diverse ethnic background and cultural settings (the participating countries included India, Oman, Ghana, Brazil, Norway and United States), the WHO introduced new growth charts. The WHO recommends their universal use.
 - The contention behind this recommendation is that differences in children's growth upto five years of age are more influenced by feeding practices, environment and healthcare rather than the genetic or ethnic factor.
 - In other words, children born anywhere in the world and given the optimum start in life have the potential to grow within the same range of height and weight.

Figures 3.21 to 3.30 present the IAP-WHO growth charts.

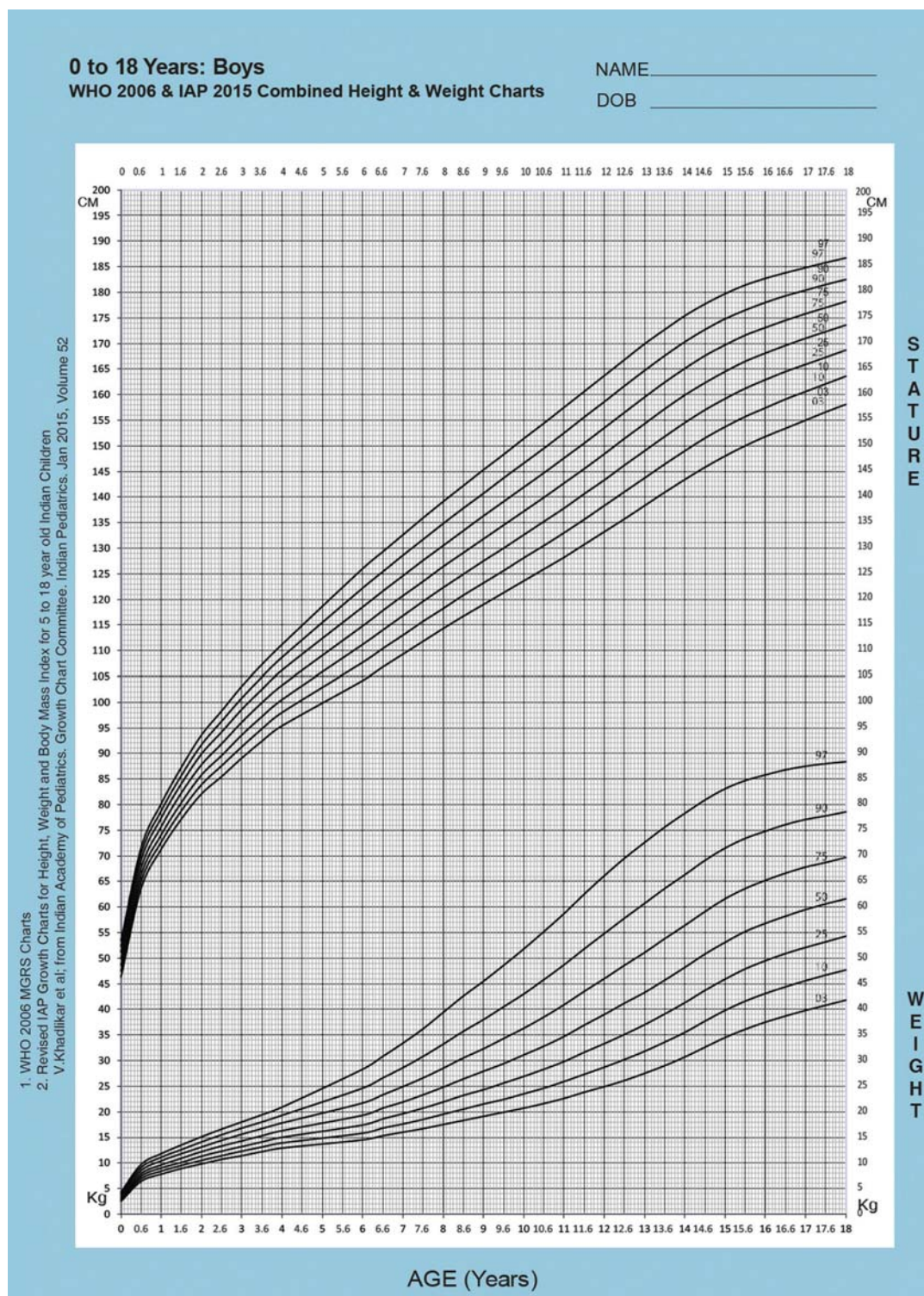


Fig. 3.21: 0 to 18 years—boys.

0 to 18 Years: Girls

WHO 2006 & IAP 2015 Combined Height & Weight Charts

NAME _____

DOB _____

1. WHO 2006 MGRS Charts
 2. Revised IAP Growth Charts for Height, Weight and Body Mass Index for 5 to 18 year old Indian Children
 V.Khadlikar et al; from Indian Academy of Pediatrics. Growth Chart Committee. Indian Pediatrics. Jan 2015, Volume 52

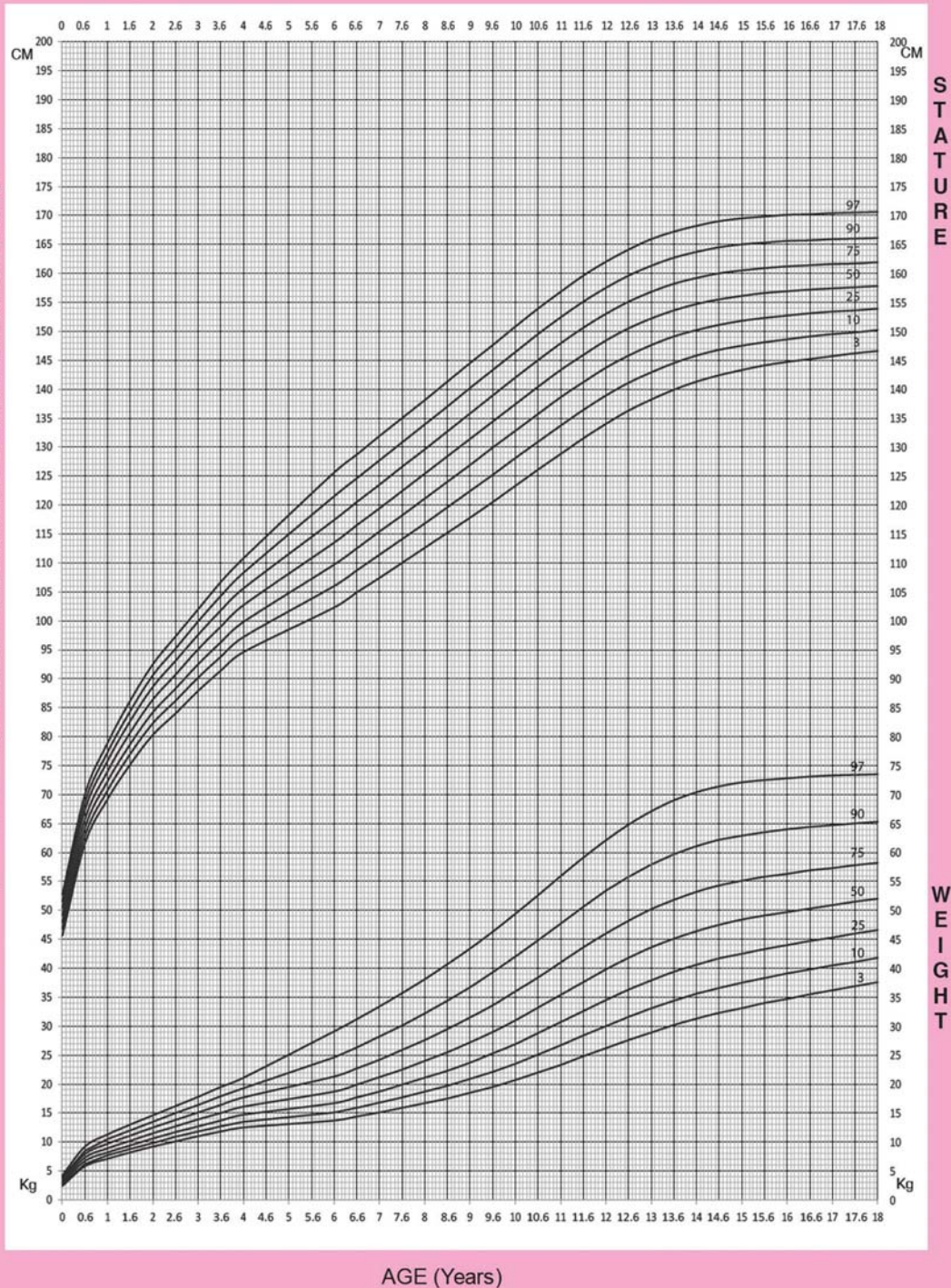


Fig. 3.22: 0 to 18 years—girls.

5 to 18 Years : IAP Boys Body Mass Index Charts

Name _____
 DOB _____

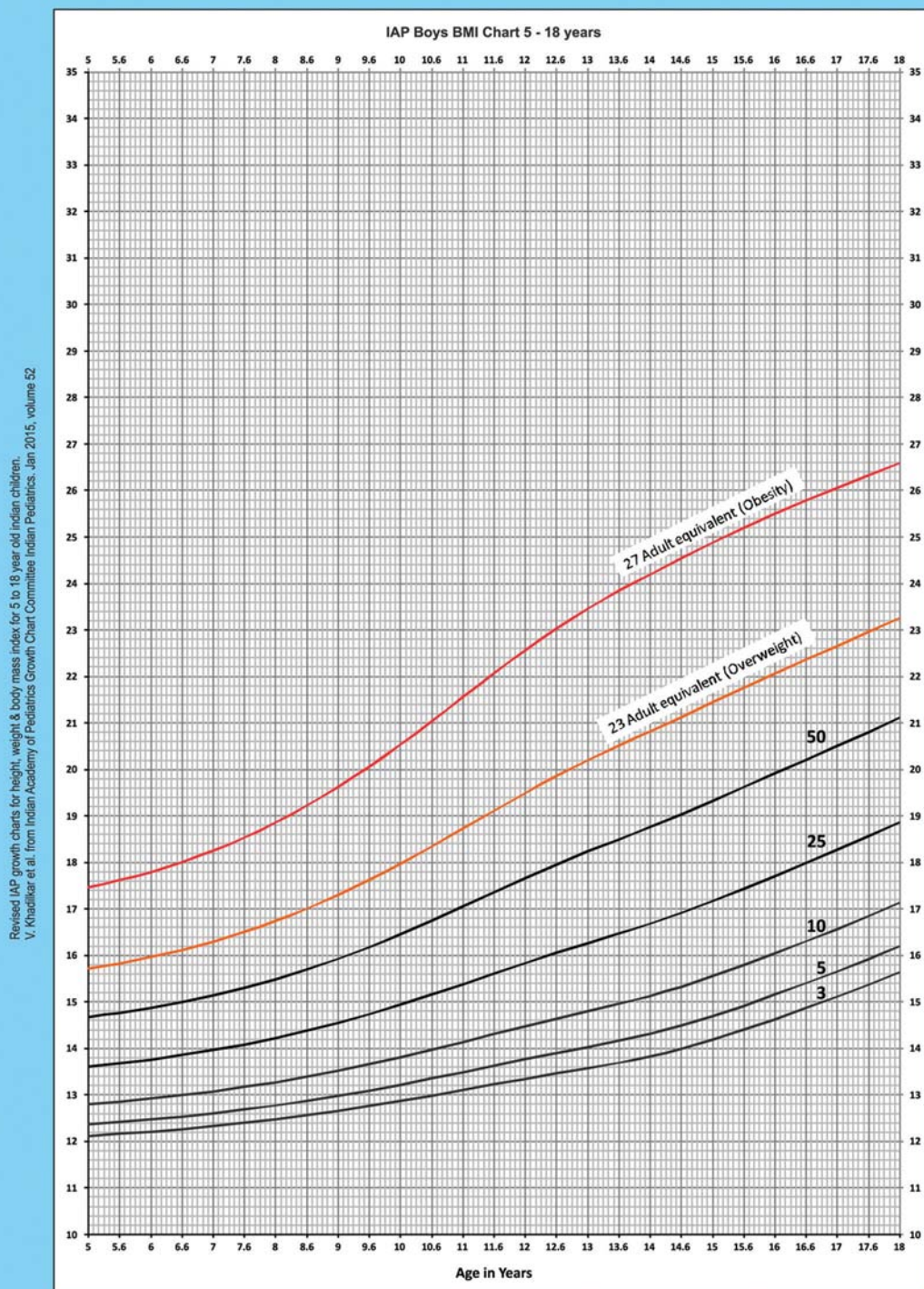


Fig. 3.23: 5 to 18 years: IAP boys body mass index charts.

5 to 18 Years : IAP Boys Height and Weight Charts

Father's Height _____, Mother's Height _____, Target Height _____

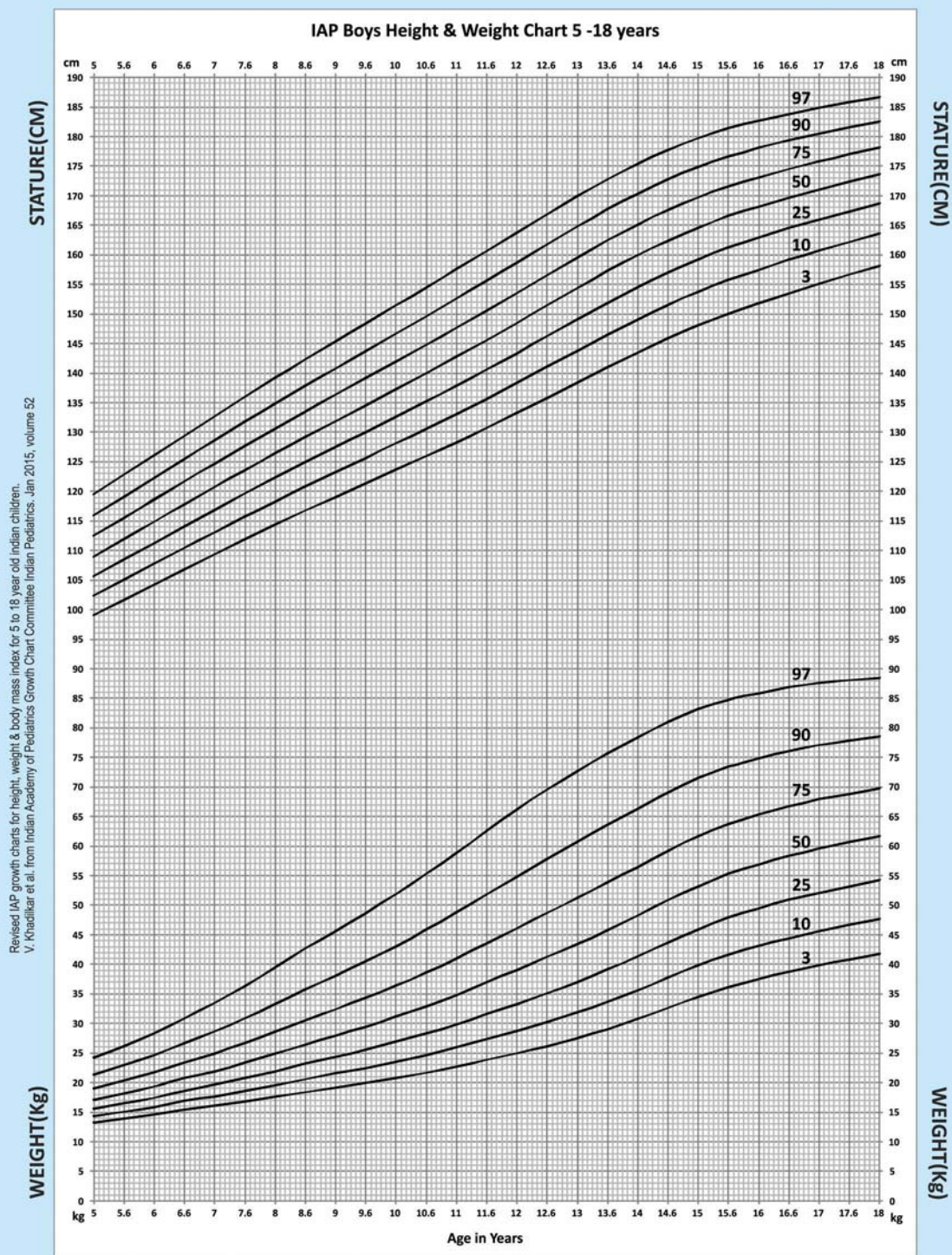


Fig. 3.24: 5 to 18 years—IAP boys height and weight charts.

5 to 18 Years : IAP Girls Body Mass Index Charts

Name _____
 DOB _____

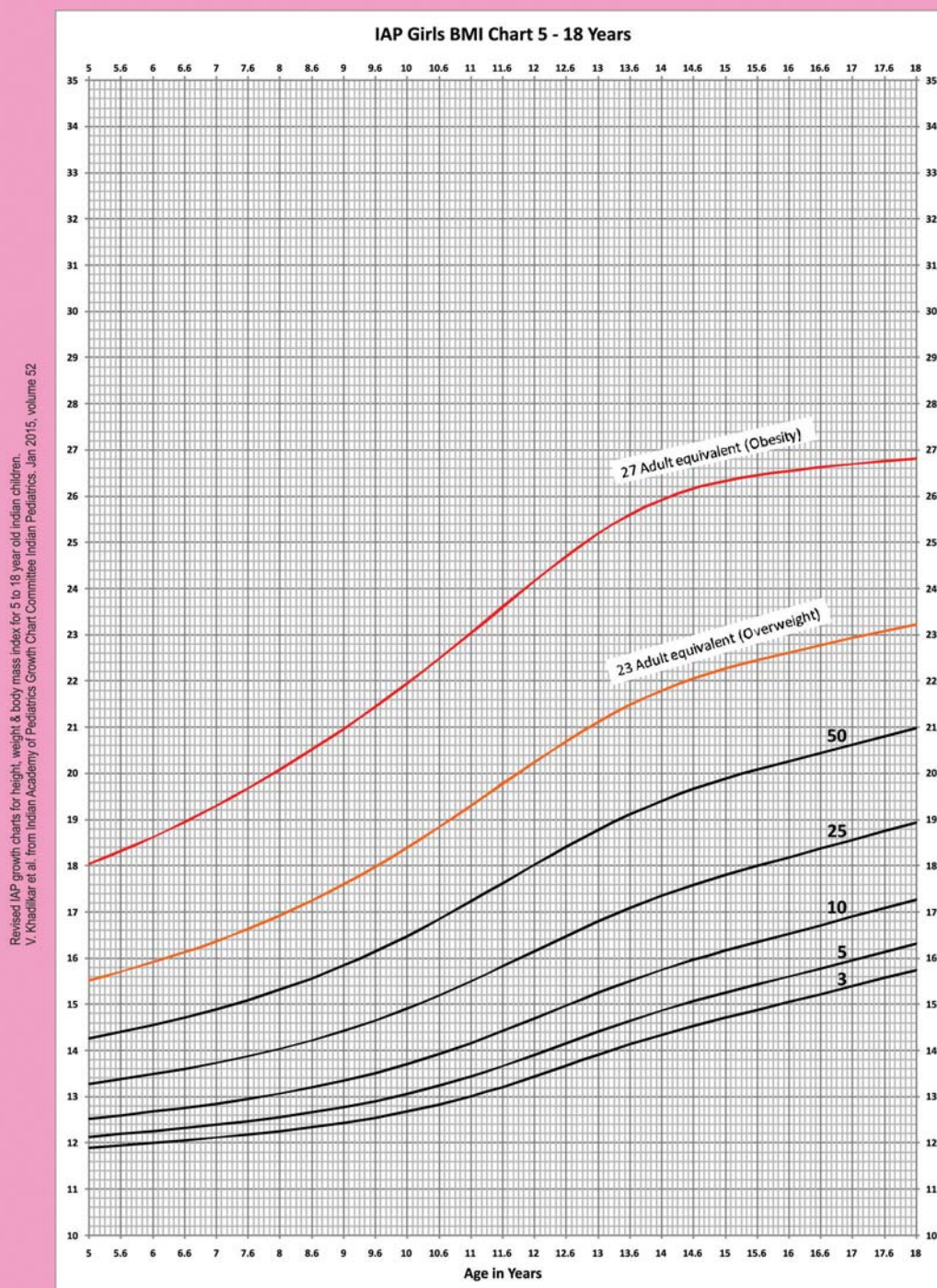


Fig. 3.25: 5 to 18 years—IAP girls body mass index charts.

5 to 18 Years : IAP Girls Height and Weight Charts

Father's Height _____, Mother's Height _____, Target Height _____

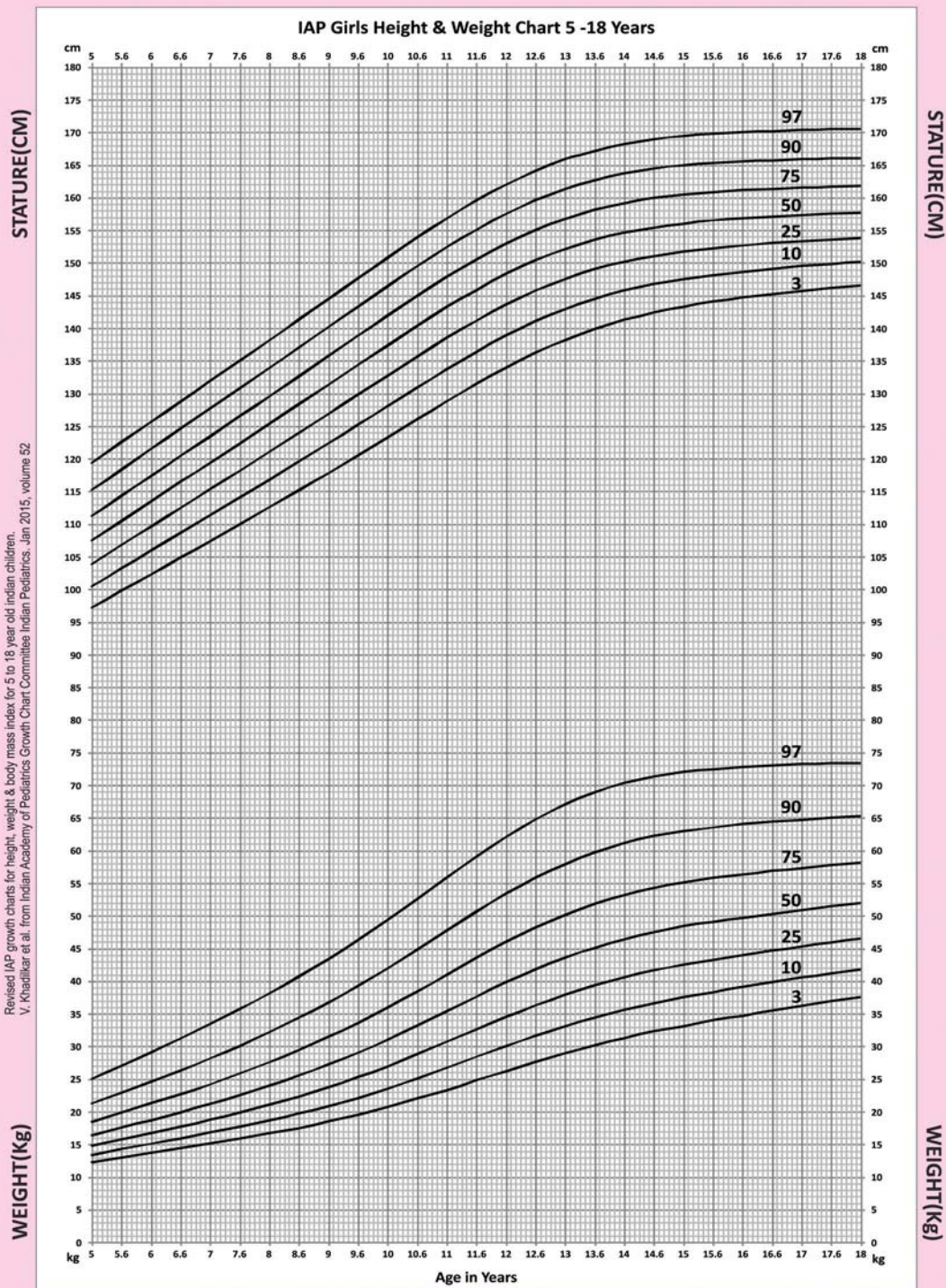


Fig. 3.26: 5 to 18 years—IAP girls height and weight charts.

0 to 5 Years : WHO Boys Length/Height, Weight and Head Circumference Charts (Z Scores are in Parenthesis)

Name : _____

DOB : _____

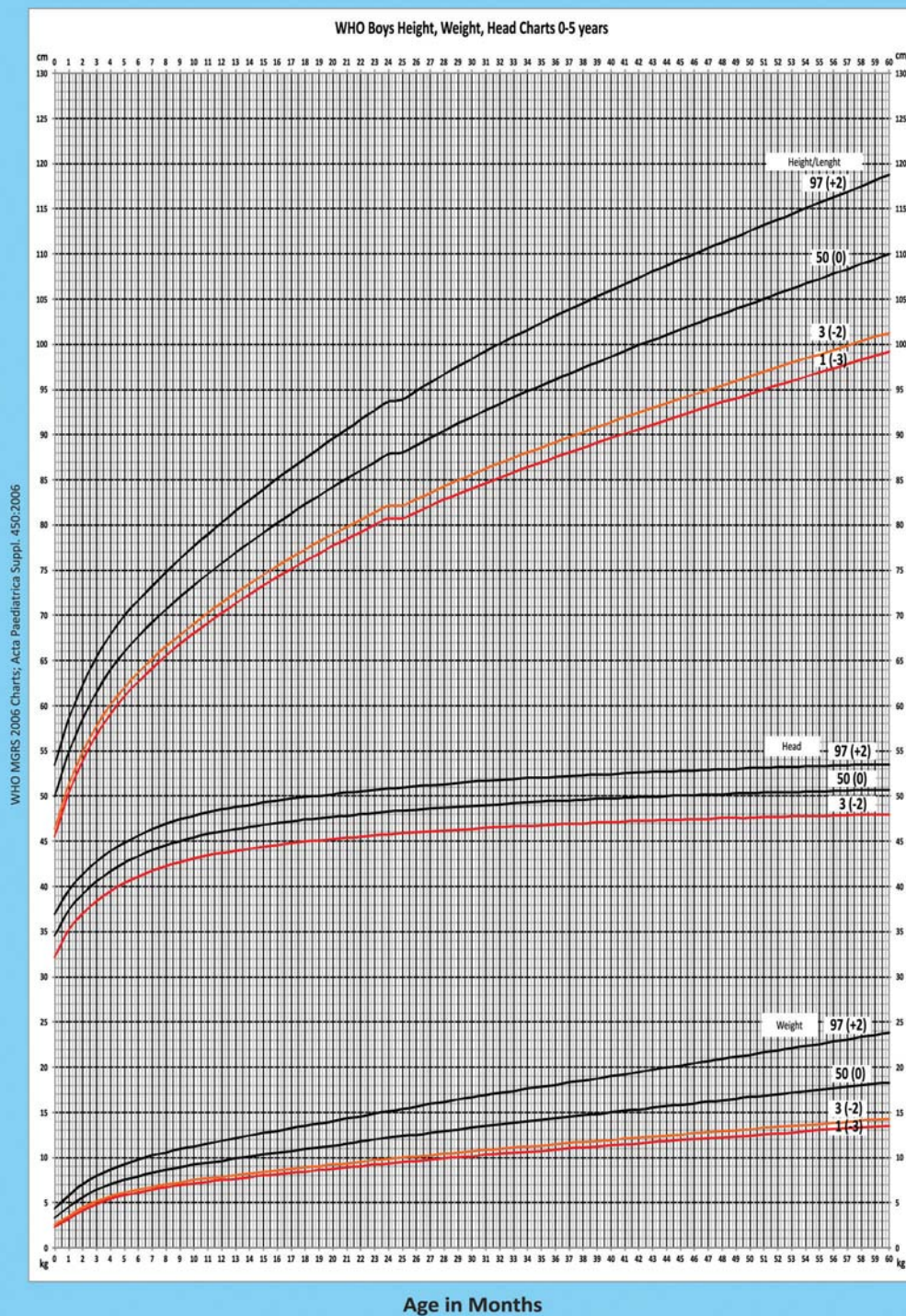


Fig. 3.27: 0 to 5 years—WHO boys length/height, weight and head circumference charts.

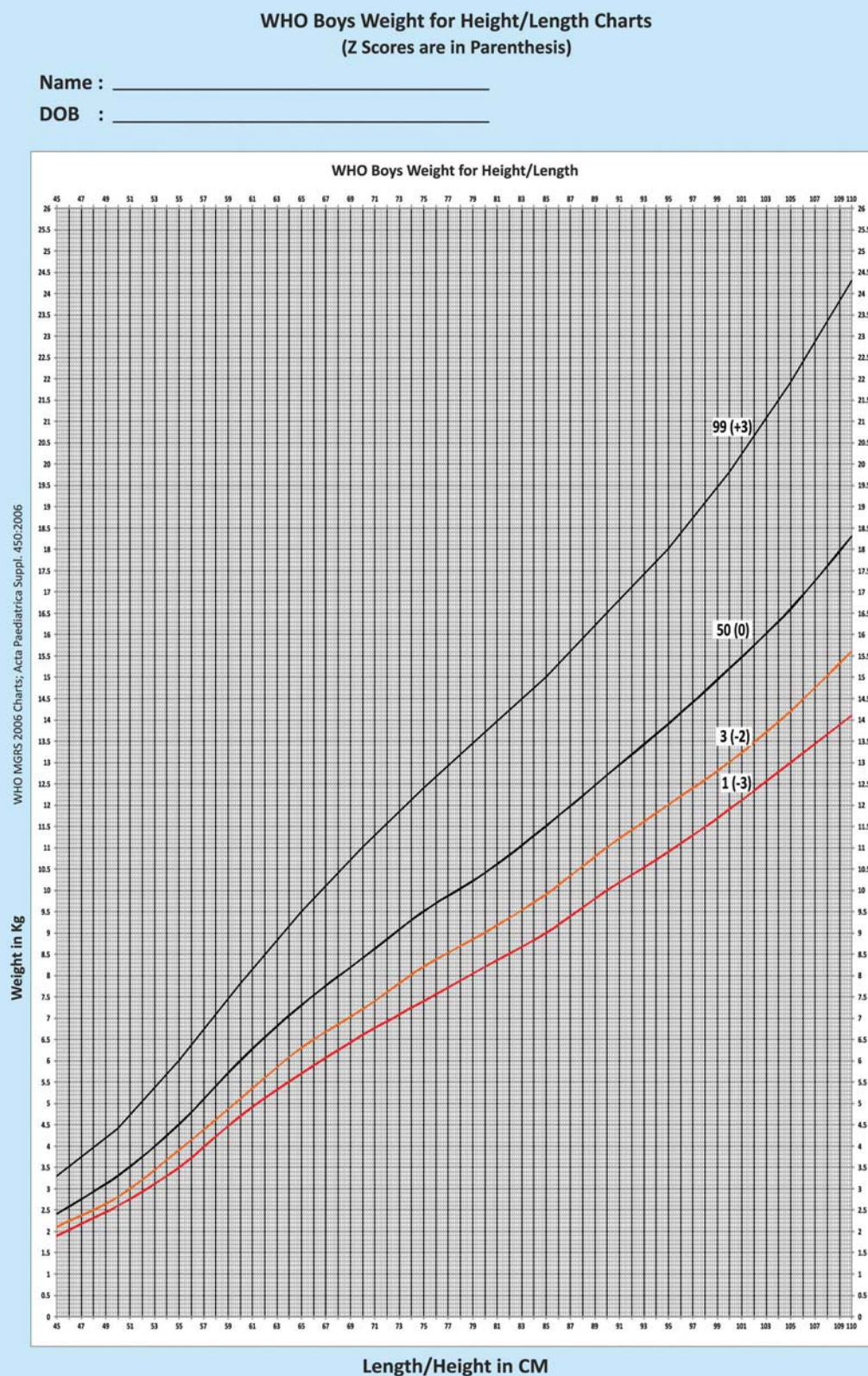
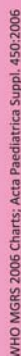


Fig. 3.28: WHO boys weight for height/length charts.

Name : _____
DOB : _____



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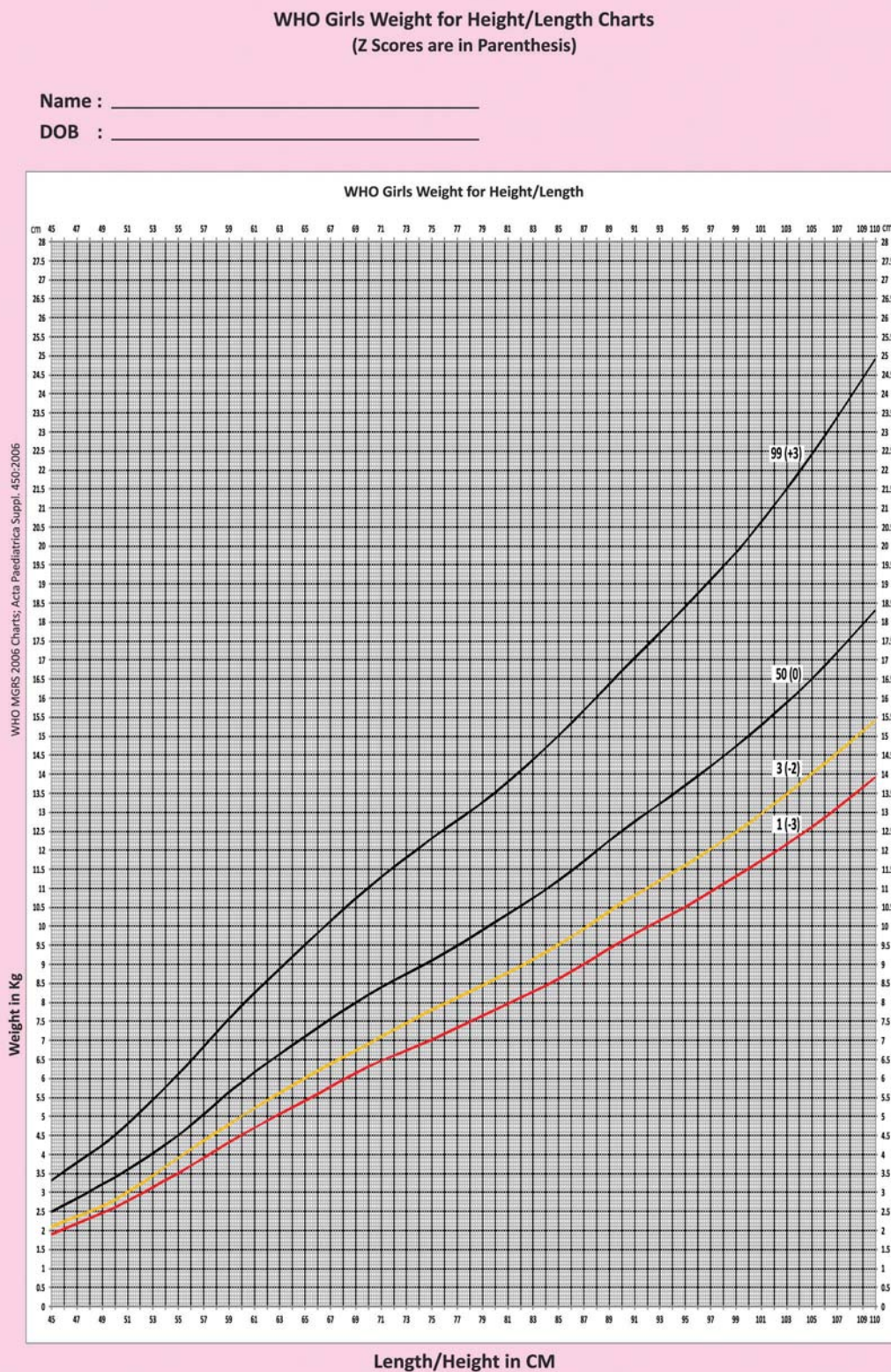


Fig. 3.30: WHO girls weight for height/length charts.

Multiple Choice Questions

- Spot the wrong entry:
 - The infant doubles his birth weight around 5 months of age
 - The infant triples his birth weight around 11–12 months
 - The infant's weight is 4 times the birth weight at 4 years
 - The infant triples his birth length at 12 years
- What is the single most useful tool for assessment of growth and nutritional status in newborns and infants on an ongoing basis?
 - Infantometer
 - Shakir tape
 - Quetlet index
 - Growth chart
- The first permanent tooth to erupt is:
 - Incisor
 - Canine
 - Premolar
 - Molar
- Most frequent condition in which delayed dentition occurs is:
 - Congenital hypothyroidism
 - Rickets
 - Down syndrome
 - Hurler syndrome
- An overwhelming proportion of brain growth occurs:
 - In adolescence
 - In preadolescence
 - Around 5 years
 - In first 2 years
- At what age does the child shows 2 carpal bones in X-ray of wrist?
 - 6 months
 - 1 year
 - 2 years
 - 3 years

Answers

1. C 2. D 3. A 4. A 5. D 6. B

Clinical Problem-solving

Review 1

A 1-year-old child has just 2 milk teeth. His weight is 10 kg and length 76 cm. He stands without support and walks with support. Vision, speech and hearing appear normal.

- What is his approximate developmental age based on the available parameters?
- Should "just 2 milk teeth" at 1 year in this child be considered abnormal?
- Could it be familial?

Review 2

A 10-month-old infant of well-placed and educated parents presents with "speech limited to monosyllables ("ma", "pa", "da", "ba" rather than mama, papa, dada, baba)" which is the cause of considerable anxiety for the parents. His other milestones (gross motor, fine motor, social/adoptive, language, hearing, etc.) appear normal.

- Should the delay in acquisition of bisyllables by 10 months indeed be a source of concern?
- What should be done in such a situation?
- Any role of parents in this area?

Answers

Review 1

- His developmental age comes to around 1 year which is in keeping with child's chronological age.
- No. Delayed eruption of teeth in an otherwise normal child (both first tooth as well as other teeth) is usually a normal variation. There is no evidence of such etiological conditions as poor nutrition, rickets, osteogenesis imperfect or ectodermal dysplasia in this infant.
- Yes, familial delay is a good possibility. It is relevant to obtain history of delayed dentition in the family members.

contd...

Review 2

1. Not really. Normally, most normal children develop bisyllable speech by 9 months. Yet, some infants, though normal in all ways, may take a little longer. If all else is well, it should not be a matter of anxiety.
2. The best course should be to reassure the parents and discuss with them the important points in language acquisition in simple terms.
3. Provision of sensory inputs to the child is of considerable value in assisting the child acquire skills.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS/INTERNET

1. Banerjee B. Growth and development from birth to puberty. In: Gupte S (ed): *Recent Advances in Pediatrics (Special Vol. 20: Nutrition, Growth and Development)*. New Delhi: Jaypee 2009:206–62.
2. Encyclopedia of Children's Health. Available at: <http://www.healthofchildren.com/P/Prenatal-Development.html> Accessed on: 30 July 2015.
3. Indian Academy of Pediatrics. Revised IAP Growth Charts 2015. Available at: <http://www.iapindia.org/Revised-IAP-Growth-Charts-2015.php> Accessed on: 10 Nov 2015.
4. Mukherjee D. Assessment of physical growth and development. In: Gupte S: *Recent Advances in Pediatrics (Special Vol. 7: Nutrition, Growth and Development)*. New Delhi: Jaypee 1997:18–62.

BOOKS/MONOGRAPHS

1. Goodyear AW. *Growth: Normal and Abnormal*, 4th ed. London: Smith and Smith 2013.
2. World Health Organization. *WHO Child Growth Standards*. Geneva: WHO 2006.

FAILURE TO THRIVE

DEFINITION

The term, **failure to thrive (FTT)**, is applied to infants and young children (usually upto the age of 5 years) who show failure of expected weight gain and striking lack of wellbeing. It is a descriptive and not a diagnostic term.

The essential component in FTT is sluggish weight gain compared to the peers of same age and sex.

In practice, one of the following criteria must be met:

- Weight <3rd percentile (some experts consider even <5th percentile),
- A change in the rate of growth crossing 2 major centiles (say, 75th to 50th) over a period of time.

Slow length/height gain and/or development may accompany FTT.

ETIOLOGY

Many Western authorities believe that the term is more or less synonymous with the psychosomatic growth failure or maternal deprivation syndrome. Experience in resource-poor region shows that although psychosomatic factors may play a significant role; a considerable proportion of children with FTT in these regions suffer from nutritional deprivation for one or the other reason.

By far the most common cause of failure to thrive in India is poor nutritional intake and feeding problems. A careful history would elicit this and also poverty, ignorance and conflict in the family. Thus, parental neglect too operates a great deal in its causation.

Another important cause/contributing factor in developing countries is one or more types of intestinal parasites infesting the child's gut. Yet another factor is the relatively common occurrence of tuberculosis in our infants and children. Besides this, FTT may well be because of several other organic (usually chronic) diseases.

Broadly, two categories are recognized:

1. **Extrinsic (nonorganic, psychosocial):** Poor dietary intake (especially energy).
2. **Intrinsic (organic):** Underlying medical condition and/or social and emotional deprivation. For a comprehensive list of causes of FTT, Box 4.1.

CLINICAL FEATURES

Typically, an infant with FTT is:

- Underweight for age, usually less than 3rd percentile (Fig. 4.1) with poor growth and development and cognition.

Box 4.1 Etiology of failure to thrive (FTT)

Extrinsic cause (nonorganic, psychosocial)

- **Poor dietary intake:** Maternal malnutrition, LBW erratic feeding practices.
- **Social and emotional deprivation:** CAN, inadequate infant mother bonding, unwanted child, parental disharmony, inexperienced or psychopath mother.

Intrinsic causes (organic)

- **Malabsorption:** Celiac disease, cystic fibrosis, lactose intolerance.
- **Intestinal parasitosis:** Giardiasis, ascariasis.
- **Persistent vomiting:** Pyloric stenosis, GERD
- **Metabolic:** Galactosemia, diabetes mellitus, congenital adrenal hyperplasia.
- **Chronic illnesses:** Congenital heart disease, asthma, ICC.

Abbreviations: CAN, child abuse and neglect; GERD, gastroesophageal reflux disease; LBW, low birth weight; ICC, Indian childhood cirrhosis.



Fig. 4.1: Failure to thrive. This 3-years-old weighed only 9.5 kg. Following an attack of bronchopneumonia, his weight gain had further slowed down. The gain was just 1.5 kg in 2 years.

- Small in size with expressionless facies, poor gross motor activity, delayed vocalization and poor response.
- Usually remains absorbed in thumb-sucking.
- Beyond infancy, the child suffering from FTT is underweight, thin and inactive.

DIAGNOSIS

Clinical Work-up

It comprises of good history, physical examination, growth chart and observation concerning parent-child interaction. All attempts should be made to find out the psychosocial cause of FTT as well as deficiency of dietary intake.

Box 4.2 Degree of failure to thrive (FTT)**Based on weight for age**

- Weight for age 75–90% of expected: Mild FTT
- Weight for age 60–74% of expected: Moderate FTT
- Weight for age <60% of expected: Severe FTT

Based on weight for height

- Weight for height 80–90% of expected: Mild FTT
- Weight for height 70–80% of expected: Mild FTT
- Weight for height 70% of expected: Mild FTT

Based on length/height for age

- Length/height for age 90–95% of expected: Mild FTT
- Length/height for age 85–90% of expected: Mild FTT
- Length/ height for age 85% of expected: Mild FTT

Degree of FTT may be determined employing the weight for age criteria as shown in Box 4.2. Additionally, weight for height and length for height as such may also be used for severity grading.

INVESTIGATIONS

- **Routine:** In most cases, routine investigations such as complete blood profile (CBP), erythrocyte sedimentation rate (ESR), urine, stool microscopy for ova and cysts (at least for three consecutive days) suffice.
- **Special:** In select cases (especially in whom organic cause is expected), chest X-ray, liver function test (LFT), kidney function tests and serum electrolytes may be warranted.

TREATMENT

Nutritional rehabilitation (Fig. 4.2) is the mainstay of treatment, though attention to psychosocial factors and organic cause, if present, should be in place.

After preliminary screening, including meticulous stool microscopy on at least three successive days, the child should be put on trial of feeding for a minimum of two weeks. If workable, it should be done after admitting the child to the hospital (Box 4.3).

During this period, it must be ensured that the child gets enough food. At the same time, intestinal parasites, if detected in stools/strongly suspected, should be treated.

If this line of management yields unsatisfactory results, the child needs to be further investigated on rather sophisticated lines for the exact etiological diagnosis.

Attention should be directed to the emotional needs of the child and in improving parent-child relationship as also in removing the conflicts.

FOLLOW-UP

Failure to thrive children need a good follow-up with emphasis on growth monitoring. Despite an improvement in

physical growth (weight and length/height), quite a proportion of them may lag behind in cognition and behavioral and emotional development.

LONG-TERM CONSEQUENCES (SEQUELAE)

- Growth retardation
 - Developmental retardation
 - Learning difficulties.
- Risk of long-term consequences is more in nonorganic FTT than in organic FTT where the etiologic diagnosis and appropriate treatment is delayed.

SHORT STATURE**DEFINITION**

Short stature is defined as length/height:

- Less by more than 2 standard deviations (SD) of mean for age and sex,
 - Below 3rd percentile for age and sex.
- In addition, the height velocity is usually <25th percentile for age and sex.

CLASSIFICATIONS

- Based on body proportions:
 - Proportionate
 - Disproportionate

This is the most widely used classification.
- Based on pathology:
 - **Physiological:** Familial, constitutional
 - **Pathological:** Systemic diseases, chromosome disorders, endocrinal disorders, skeletal dysplasia's, etc
- Based on intrinsic or extrinsic defect:
 - **Primary short stature** is usually due to an intrinsic defect in the skeletal system as a result of some genetic or prenatal damage (say, intrauterine growth restriction {IUGR}). Here, potential for normal bone growth is impaired though skeletal age is unaffected. Main effect is on diaphyseal growth.
 - **Secondary short stature** is characterized by the impairment of bone age and height to the same extent. Here, the potential for reaching the adult height is subject to availability of proper treatment.
- Based on endocrine or nonendocrine background.
- Based on prenatal or postnatal background.

Table 4.1 gives a widely used etiologic classification of short stature.

SALIENT FEATURES OF IMPORTANT TYPES**Constitutional Short Stature**

More appropriately termed *constitutional growth delay*, this condition should be regarded as a sheer variant of normal growth. Here, bone age is consistent with height age, but less than the chronological age. The onset of puberty is delayed. Eventually, however, adult height and sexual maturation are normal.

Box 4.3 Failure to thrive: Indications for hospitalization

- Trial of feeding
- Second-line investigations for organic cause(s)
- Suspicion of maltreatment, child abuse and neglect
- Severe malnutrition
- Lack of catch-up growth.

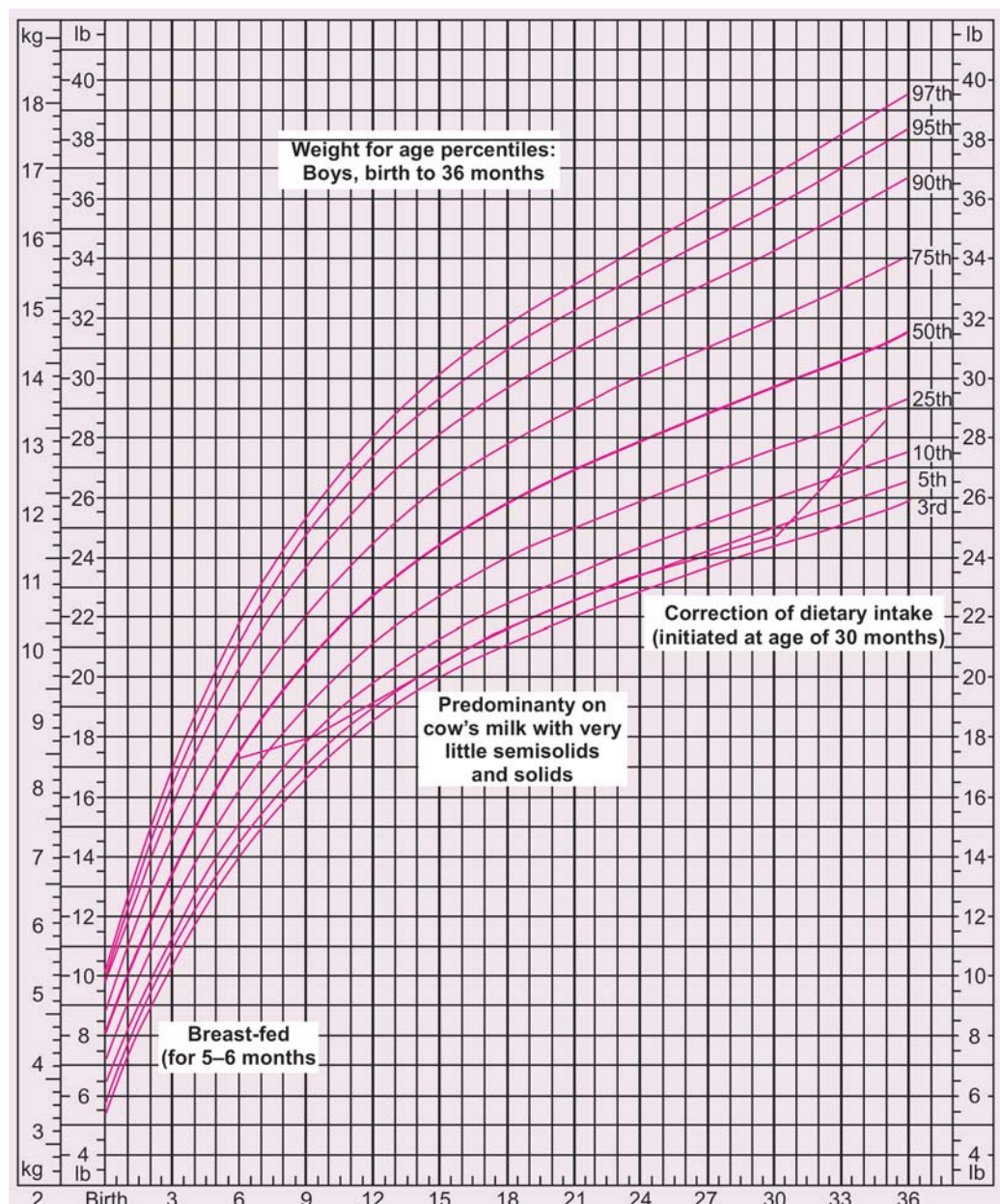


Fig. 4.2: The growth chart depicting failure to thrive. Note the poor weight gain between age 6 and 18 months when the child was predominantly on cow's milk with very little semisolids and solids. Correction of dietary intake resulted in restoration of weight gain.

Table 4.1: Etiology of short stature based on body proportions

Proportionate short stature

- **Normal variants**
 - Constitutional
 - Familial/genetic
- **Prenatal origin**
 - **Intrauterine growth retardation (IUGR):** Maternal diabetes, toxemias, infections teratogens (alcohol, nicotine, etc.)
 - **Dysmorphic syndromes:** Silver-Russell syndrome
 - **Chromosomal anomalies:** Turner's syndrome, Down's syndrome.
- **Postnatal origin**
 - **Nutritional:** Chronic malnutrition spread over a prolonged period
 - Organic diseases
 - **Gastrointestinal:** Malabsorption syndrome in the form of celiac disease, endemic tropical sprue or cystic fibrosis, heavy intestinal parasitism, cirrhosis of liver, congenital megacolon
 - **Cardiovascular:** Congenital heart disease, rheumatic heart disease
 - **Respiratory:** Pulmonary tuberculosis, bronchial asthma, bronchiectasis, cystic fibrosis

contd...

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- **Hematologic:** Chronic iron deficiency anemia (IDA), thalassemia, sickle-cell anemia
- **Endocrinal:** Pituitary dwarfism, hypothyroidism, hypogonadism, dysmorphic syndromes, precocious puberty, pseudohypoparathyroidism, diabetes mellitus, Cushing's syndrome, Laurence-Moon-Biedle's syndrome Frohlich's syndrome
- **Renal:** Renal rickets from chronic renal failure and tubular disorders
- **Chronic infection:** Tuberculosis, malaria, syphilis, heavy parasitic infestation, *Helicobacter pylori* infection
- **Drug induced:** Prolonged use of anabolic steroids or corticosteroids.
- **Psychosocial:** Emotional deprivation, parental neglect, child abuse and neglect.

Disproportionate short stature

- **Short limbs:** Congenital hypothyroidism, achondroplasia, osteogenesis imperfecta, amelia, rickets*
- **Short trunk:** Mucopolysaccharidosis (Morquio's disease), spondyloepiphyseal dysplasia mucopolipidosis, caries spine, hemivertebrae, rickets*

* Rickets figures in both since it may cause gross deformities (shortening) of trunk and legs.

Facial features may be somewhat immature. Frequently, one or both parents or other close family members have a history of short stature in childhood, delayed puberty and finally, normal stature.

Classically, such a child is born with normal weight and length. Growth remains normal for the first 4–12 months. Then, it slows down until 2–3 years age when it becomes normal, but at a relatively lower level of normal (5 cm or little more per year compared to 6–7 cm per year in a normal child). Puberty is delayed too. Nevertheless, the final outcome is satisfactory as normal adult height as well as sexual development is attained. In constitutional short stature, human growth hormone and gonadotropin levels are normal.

Figure 4.3 shows comparison of the length/height curves in idiopathic and familial/genetic short stature.

Primordial Dwarfism

Here, IUGR is responsible for short stature. It is claimed that arrest of the fetal growth early in pregnancy results in reduction in number of cells. As a consequence, growth potential in the postnatal period is diminished. Bone age is usually normal, corresponding to the chronological age, or somewhat retarded. Growth velocity may be moderately affected. The child, as a rule, has a slender physique with sharp, fine facies and craniofacial disproportion.

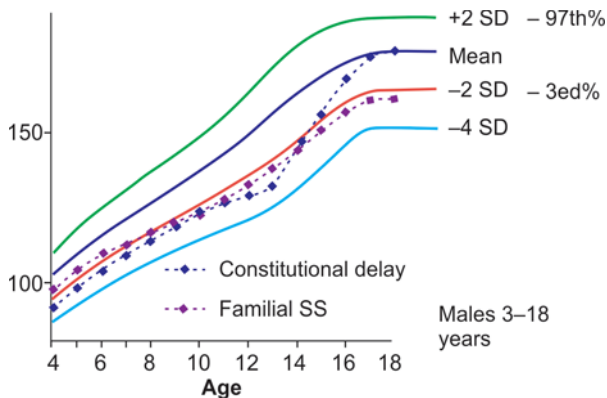


Fig. 4.3: Constitutional vis-à-vis familial short stature. Note that in constitutional short stature (SS), growth curve slows down towards the end of first year, remaining below 2SD until puberty. At puberty, it catches up to reach the mean for age. That does not happen in familial short stature where the curve consistently remains below 2SD.

Associated learning disabilities are common. Usually, prognosis for adult height is poor, particularly in the subjects who are small for gestational age.

There is an evidence that most of the short children with history of low birth weight secondary to IUGR have growth hormone deficiency.

Russell-Silver syndrome (also called **Silver-Russell syndrome**) is characterized by short stature, small triangular facies, frontal bossing, scanty subcutaneous fat, short and incurved fifth finger with or without hemi-hypertrophy in a child who had low birth weight for gestational age.

Nutritional Stunting

Chronic protein energy malnutrition (PEM) or iron deficiency anemia (IDA) of long standing, particularly when it is not gross enough to cause overt disease, leads to stunting in height as an adaptation reaction (Fig. 4.4).

The child often appears to be all right since wasting may not be present and stunting is appreciated only once the actual age is revealed. Bone age is, as a rule, less than the chronological age.

Catch-up growth, though incomplete, is expected in these children once the nutritional rehabilitation is satisfactorily achieved.



Fig. 4.4: Short stature. Note the remarkable stunting in this 14 year-old boy against his 11 year-old sister.

70 Emotional Deprivation

The so-called **psychosocial dwarfism**, **deprivation dwarfism** or **reversible hyposomatotropism** cause short stature through functional hypopituitarism. These children have perverted appetite, enuresis, encopresis, insomnia, crying spasms and sudden tantrums. They may be passive or aggressive. History of upset mother-child or family relations provides a clue to the diagnosis. Bone age is little delayed or just normal. Body proportions are normal.

With the provision of adequate emotional warmth and security, these children show catch-up growth.

Chronic Systemic/Visceral Diseases

Short stature is a feature of most chronic visceral diseases (malabsorption syndrome, inflammatory bowel disease, congenital heart disease, renal tubular acidosis, chronic renal failure, occult renal disease, diabetes mellitus, thalassemia and bronchial asthma) as also chronic infections (tuberculosis, chronic intestinal parasitosis, malaria, kala-azar, syphilis and pyelonephritis). As a matter of fact, the retardation is in total growth.

Recently, it is being increasingly recognized that short stature may be the solitary manifestation in certain cases of celiac disease. The implication of this observation, particularly in areas where this disease occurs is significant.

Endocrinopathies

Short stature accompanying endocrinal disorders are conspicuous by the presence of a remarkable delay in bone age.

- **Growth hormone deficiency (pituitary dwarfism)** should be suspected if the subject's appearance is infantile, bone age is considerably retarded and the growth velocity is less than 4 cm per year. Diagnosis is confirmed by testing growth hormone levels after provocative stimulation (say exercise, insulin, propranolol, arginine, L-3, 4-dihydroxyphenylalanine L-DOPA). Growth hormone deficiency is an uncommon cause of short stature. It may occur in isolation or in association with other pituitary hormones when the condition is termed **panhypopituitarism**.

- **Hypothyroidism** is easily recognized when the clinical profile of a full-blown case is classical. What needs to be specially borne in mind is that hypothyroidism can present with short stature and growth retardation alone. Body proportions remain infantile. Bone age shows remarkable retardation. Diagnosis must be confirmed by demonstrating low thyroxine (T_4) and high thyroid stimulating hormone (TSH) levels.
- **Cushing syndrome** may result from exogenous steroid therapy or secondary to a pituitary or adrenal tumor. Despite being overweight, the child has growth retardation, short stature and delayed epiphyseal maturation. Remaining features of the syndrome, such as moon facies, abdominal striae, plethora, hypertension and reduced glucose tolerance may be present.
- **Diabetes mellitus** is usually accompanied by growth retardation, particularly when it is poorly controlled. There may be history of polyuria, nocturnal enuresis,

polydipsia and polyphagia. Urine and blood sugar clinch the diagnosis.

Skeletal Disorders

Disproportionate short stature should arouse suspicion of skeletal dysplasia such as achondroplasia, pseudoachondroplasia, osteogenesis imperfecta, spondyloepiphyseal dysplasia, profound rickets, hemivertebrae, caries spine or mucopolysaccharidosis (MPS) such as Morquio's and Hurler's syndrome.

Chromosomal Disorders

It is important to consider Turner's syndrome (classical pattern XO) in the differential diagnosis of short stature in girls. Remaining features of the condition include webbing of neck, edema of lower limbs, widely placed nipples, cubitus valgus, coarctation of aorta and a short fourth metacarpal as also absence of secondary sex characters.

Noonan's syndrome is just the prototype of Turner's syndrome in girls as well as boys with the exception that chromosomal count is normal and, in place of coarctation of aorta, pulmonary stenosis with or without atrial septal defect (ASD) is more common.

Genetic Disorders

Several genetic disorders may be accompanied by short stature:

- Mucopolysaccharidosis
- Aminoaciduria
- Galactosemia
- Glycogen-storage disease
- Renal tubular acidosis.

Idiopathic Short Stature

Here, the height is short and growth velocity is less. Neither the parents are short nor is there any systemic disease. The etiology remains unknown despite clinical and investigative work-up. Some of these cases may have growth hormone deficiency because of a peculiar gene (SHOX). This deficiency is, somehow, not demonstrable.

DIAGNOSTIC APPROACH

A stepwise diagnostic approach, beginning with history and physical examination with special reference to anthropometry and culminating with sophisticated (Level III) investigations, depending on the individual merits of each case (Box 4.4) is important in arriving at the etiologic diagnosis of short stature.

Box 4.4 Stepwise diagnostic approach to short stature

- Detailed history and examination, including anthropometry
- **Investigations:**
 - **Level I:** Complete blood profile (CBP), urine, stool, skeletal X-ray(s) for bone age, buccal smear.
 - **Level II:** Thyroid profile, karyotyping.
 - **Level III:** Celiac serology, provocative growth hormone testing, serum insulin-like growth factor-1, insulin-like growth factor binding protein-3 levels, magnetic resonance imaging (MRI) brain, etc.

History and Physical Examination

A good history and physical examination are important in evaluating a case of short stature (Table 4.2).

Anthropometry

- **Height:** Accurate measurement of supine length less than 2 years and height at and beyond two years are important.
- **Height velocity:** It is more useful than a single recording of the height. It is calculated from at least two accurate readings at a gap of 6 months (preferably one year). A velocity of less than 4 cm per year between 5 years of age and adolescence is considered pathological. For younger children, it varies with age—15 cm for 0–6 months, 7 cm for 6–12 months, 10 cm for 1–2 years, and 5 cm for 2–4 years.
- **Body proportions:** These are considered to be the most accurate index of height. Upper segment/lower segment ratio (short-limb short stature) is increased in hypothyroidism, achondroplasia (Fig. 4.5), rickets, certain mucopolysaccharidosis (MPS) (say Hurler syndrome and Turner syndrome). The ratio is decreased (short-trunk short stature) in spondyloepiphyseal dysplasia, certain MPS (Morquio's syndrome), rickets involving vertebral column, etc.
- **Span:** Measurement from midfinger tip to midfinger tip in case of fully outstretched arms and hands is increased (more than height) in spondyloepiphyseal dysplasia and Morquio's syndrome and rickets involving vertebral column.
- **Midparental height:** A genetic component, it gives child's own potential to obtain his target height. It is

Table 4.2: History and physical examination as a clue to diagnosis of short stature

Information	Diagnostic probability
History	
Delayed puberty in parents	Constitutional short stature
Low birth weight (SGA, IUGR)	Primordial dwarf
Lethargy, constipation, delayed milestones, intellectual disability	Congenital hypothyroidism
Chronic diarrhea with steatorrheic stools following initiation of semisolids	Celiac disease
Recurrent respiratory infections with chronic recurrent diarrhea, FTT despite good dietary intake	Cystic fibrosis
Chronic dietary deficiency	Nutritional dwarfing/stunting
Visual difficulties, headache, vomiting	IC SOL (craniopharyngioma)
Maltreatment/CAN	Psychosocial short stature
Hypoglycemia, icterus, micropenis in a neonate	Hypopituitarism
Polyuria	Chronic renal disease
Progressive vision problems, obesity	Laurence-Moon-Biedl syndrome
Physical examination	
Short limb	<ul style="list-style-type: none"> • Chondrodystrophy • Achondroplasia • Multiple epiphyseal dysplasia • Congenital hypothyroidism • Turner/Noonan syndrome • Rickets (genu valgum/varus) • Mucopolysaccharidosis (Hurler/Hunter syndrome)
Short trunk	<ul style="list-style-type: none"> • Spondyloepiphyseal dysplasia, mucopolysaccharidosis (Morquio syndrome) • Severe anomalies of vertebral column: <ul style="list-style-type: none"> ▪ Congenital: Kyphosis, scoliosis, lordosis ▪ Acquired: Severe rickets (involving vertebral column)
Frontal bossing, small triangular facies, sparse subcutaneously fat, short and incurved 5th finger, hemihypertrophy, LBW	Silver-Russell syndrome
Large head with dysmorphic facies, arms failing to reach upper thighs	Achondroplasia
Intellectual disability, repulsive dull facies, sluggishness, hypotonia	Hypothyroidism
Proportionate short stature with nearly normal IQ, round head, short small, but broad face, small saddle-shaped and depressed nose, infantile mandible and chin	Congenital hypopituitarism (pituitary dwarf)
Obesity (central) with moon facies	Cushing syndrome
Hypertension	Chronic renal disease

Abbreviations: SGA, small gestational age; IUGR, intrauterine growth retardation; FTT, failure to thrive; CAN, child abuse and neglect; IC SOL, intracranial space-occupying lesions; LBW, low birth weight; IQ, intelligence quotient.



Fig. 4.5: Achondroplasia. Disproportionate short stature in a child with achondroplasia. Note the short extremities (maximum brunt on proximal segment, i.e. rhizomelia).

determined as mean of father and mother's heights plus 13 in case of boys and minus 13 in case of girls as described in Chapter 3 (Normal Growth).

The target range is obtained by plotting on the growth chart where the two points 8 cm above and below the target height at adult equivalent age, i.e. 18–20 years. This represents the 3rd and the 97th centile for the said child. The 3rd and 97th centiles are constructed by tracing lines backward to match the child's current age,

If weight is less proportionally reduced than height, nutritional deprivation must be seriously considered. On the contrary, if weight is nearly normal, but height is significantly less, hypothyroidism must be seriously considered. Growth hormone deficiency and hypercorticism also figure in the differential diagnosis.

Sexual Maturity Rating (Pubertal Staging)

This is done by Tanner's method described in Chapter 7 (Adolescent Medicine). Children with delayed puberty and short stature should arouse suspicion of sex chromosomal anomalies. In Turner syndrome, the child is likely to end up with short stature despite timely onset of puberty. In late maturers, both short stature and delayed puberty coexist. These late maturers eventually attain better heights compared to early maturers.

Investigations

Level I

Bone age assessed through radiological examination of certain bones and then comparing the appearance and fusion of epiphyseal centers with standard normal radiographs for different ages is of considerable value.

In infancy, knee, wrist and hand, and in later years elbow, wrist and hand are appropriate sites for bone age

Box 4.5 Interpreting bone age in short stature

Normal

Familial

Delayed (retarded)

- Constitutional
- Hypothyroidism
- Growth hormone deficiency
- Cushing syndrome
- Chronic malnutrition
- Chronic systemic diseases
- Delayed adolescence/puberty
- Turner's syndrome
- Noonan's syndrome.

Advanced

- Genetic and chromosomal disorders (Down syndrome)
- Sexual precocious puberty
- Obesity
- Hyperthyroidism
- Adrenal hyperplasia.

determination. Interpretation of bone age in terms of cause of short stature is presented in Box 4.5. With the availability of assessment mentioned so far, the following guidelines are suggested:

- If height age falls within 2 years of the chronological age, the subject need not be considered to have short stature.
- If height age is less than the chronological age and the bone age is equal to height age, slow growth—in other words, constitutional delay is the likely cause of short stature. In this situation, the child attains his target height subsequently.
- If the height age is less than the chronological age and the bone age equal to chronological age, genetic short stature is the diagnosis. Such a child has short parents and is likely to remain short.
- If bone age is less than chronological age, one should consider constitutional growth retardation, hypothyroidism, malnutrition, growth hormone deficiency and chronic systemic disease as the cause of short stature.

Level II: Specific Investigations

Besides radiology and routine investigations, including meticulous stool examination on at least 3 successive days, it should be ascertained if there is a need for intensive workup. The indications for such a workup are listed in Box 4.6. The specific investigations are:

- Karyotyping, especially in girls in order to exclude Turner syndrome,
- Thyroid function tests.

Box 4.6 Indications for intensive work-up

- Height over 2SD less than the mean for that age.
- Growth (height) velocity less than 4 cm per year.
- Growth centile showing subnormality in relation to family stature (midparental height).
- Inappropriate bone age compared to height age and actual (chronological) age.
- Existence of characteristic features of an endocrinal cause or a syndromal state.

Table 4.3: Important differentiating features of familial, constitutional, growth hormone deficiency and hypothyroid short stature

Feature	Familial short stature	Constitutional short stature	Growth hormone deficiency short stature	Hypothyroid short stature
Bone age	Normal (consistent with chronological age)	Delayed (chronological age)	Grossly delayed	Grossly delayed
Growth velocity	Normal	Normal	Low	Low
Growth pattern	Slow from birth	Slow from infancy	Slow from infancy	Slow from birth
Adult height	Predictable	Attained late	Remains short	Remains short
H/o constitutional delay in family	Absent	Present	Absent	Absent
H/o familial short stature	Present	Absent	Absent	Absent
Birth weight/length	Low	Normal	Normal	Normal
SMR (puberty)	Normal	Delayed	Delayed	Delayed
GH	Normal	Normal	Low	Normal
Gonadotropin	Normal	Normal	Low	Variable
Treatment	Nil	Nil	Replacement therapy with GH	Replacement therapy with thyroxine

Abbreviations: SMR, standard metabolic rate; GH, growth hormone; H/o, History of.

Level III: Sophisticated Tests

- Imaging studies like ultrasound, computed tomography (CT) scan (pituitary, adrenals, pelvic organs),
- Somatomedin-C measurement,
- Cortisol, luteinizing hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), testosterone, estrogen levels,
- Malabsorption studies, especially celiac profile,
- Renal acidification test,
- Urinary aminoacidogram,
- Urinary iodine levels.

Important comparative features of familial, constitutional, growth hormone deficiency and hypothyroid short stature are presented in Table 4.3.

MANAGEMENT

Management depends on the underlying cause (Table 4.4). Even if no treatable cause is found, the situation should be explained to the parents.

GROWTH HORMONE THERAPY

Features of growth hormone therapy are highlighted in Box 4.7.

SURGICAL INTERVENTIONS

Limb-lengthening procedures are useful in select cases, say skeletal dysplasia. Occasionally, surgical excision may be indicated if short stature is secondary to a brain tumor causing hyposomatotropism.

TALL STATURE

Tall stature is defined as a height in excess by 2 SD or above 97th percentile of the mean for age and sex.

Table 4.4: Guidelines for treatment in short stature

Situation	Treatment
General	Good balanced diet, wormicidals, hematinics and zinc
Growth hormone deficiency	Replacement therapy
Hypothyroidism	Replacement therapy
Turner syndrome	Low dose estrogens, anabolic steroids, growth hormone
Systemic diseases	Specific therapy
Idiopathic	Zinc supplementation, growth hormone
Skeletal dysplasia	Limb-lengthening surgery is possible though expensive and vulnerable to morbidity
Familial	No treatment required
IUGR (primordial dwarfism/Russell-Silver syndrome)	Growth hormone, (if growth failure continues beyond 3 years)

Abbreviation: IUGR, intrauterine growth retardation.

Box 4.7 Growth hormone therapy in short stature

Established indications

Growth hormone (GH) responsiveness in cases of:

- Biochemical GH deficiency supported by stimulation test(s), after thyroid function has been shown to be normal, plus slow growth velocity,
- Idiopathic short stature with low growth velocity.

Equivocal but approved indications

- Turner syndrome,
- Primordial dwarfism—small for gestational age (SGA) infants, IUGR (Silver-Russell syndrome), if growth fails to occur by three years,
- Chronic renal failure before renal transplant,

contd...

- Prader-Willi syndrome,
- SHOX syndrome*.

Cost of therapy

Today's genetically engineered growth hormone i.e. recombinant human GH (rhGH) therapy is costly (around US \$ 4000 to 8000, i.e. INR 2.5 to 5 lakh).

Administration and dosage

- **Age:** It is mandatory to start such a therapy before 11 years of age for attaining the optimal height.
- **Dose:** Recombinant GH is administered in a daily dose of 0.03–0.1 unit/kg (SC), preferably at night, until adult height is attained. Usually, height gain is 10–12 cm in first year and 6–8 cm every year subsequently.
- **Monitoring:** GH therapy should preferably be monitored by insulin-like growth factor-1 (IGF-1) to ensure safety and efficacy of GH. Excess GH and IGF-1 exposure and malignancy are known risks of GH therapy.

Criteria for stopping

- Growth rate <2.5 cm/year
- Bone age >14 years in girls and >16 years in boys.

Adverse drug resistance (ADRs)

- Pseudotumor cerebri
- Gynecomastia
- Slipped capital femoral epiphysis
- Scoliosis (occurrence or worsening if already present)
- Reversible hypothyroidism
- Diabetes mellitus.

* SHOX is an abbreviation for the short stature homeobox containing gene. Two functional copies of the SHOX gene are required for normal growth. Its deficiency causes short stature.

ETIOLOGY

- **Genetic and chromosomal:** Familial, Marfan syndrome, homocystinuria, Klinefelter syndrome, cerebral gigantism, Beckwith-Wiedemann syndrome,
- **Endocrinal:** Congenital adrenal hyperplasia (in early stage), androgen-secreting adrenal tumors (in early stages), thyrotoxicosis, true precocious puberty, pituitary gigantism.
- **Central nervous system (CNS):** Hydrocephalus
- **Metabolic:** Homocystinuria.

Box 4.8 lists the clinical situations that may end up in tall stature in children.

APPROACH

History

A good history needs to bring out the following important information that may act as clues to etiology:

- Tall parents and close relatives.
- Child's intellectual performance.
- Any hint of precocious or delayed puberty?
- Was tall stature present right at birth or it showed rapid growth subsequently?
- Did the length/height showed sudden acceleration only recently?

Physical Examination

An accurate record of the length/height is the first and the foremost in physical workup.

Box 4.8

Clinical situations ending up in tall stature in childhood

Fetal overgrowth

- Maternal diabetes
- Cerebral gigantism
- Beckwith-Wiedemann syndrome
- Other insulin-like growth factor (IGF-II) recess syndromes.

Postnatal overgrowth

- Familial
- Cerebral gigantism
- Beckwith-Wiedemann syndrome
- Pituitary gigantism
- McCune-Albright syndrome
- Precocious puberty
- Marfan's syndrome
- Klinefelter syndrome (XXY)
- SHOX* excess syndrome
- Fragile X syndrome
- Homocystinuria.

* SHOX is an abbreviation for the short stature homeobox containing gene. Two functional copies of the SHOX gene are required for normal growth. Its excess causes excessively tall stature.

- Any evidence of raised intracranial pressure (ICP)?
- Any other neurologic signs?
- Any evidence of dysmorphism (antimongoloid slant), obesity, arachnodactyly?

Investigations

Laboratory and radiological investigations depend on the individual merit of each case.

THE OBESE CHILD

Despite the overwhelming problem of nutritional deficiencies in India and other developing countries, obesity too is encountered, especially among the infants, children and adolescents of the elite who ape the lifestyle of the West.

DEFINITION

Obesity is defined as the excessive accumulation of fat in the subcutaneous and other body tissues and parts. Whereas in case of **overweight**, body weight has increased over 110% of the standard weight (corresponding to >30 mm triceps skin-fold thickness), in obesity the increase exceeds 120% of the standard weight.

The most dependable and best parameter for screening children for obesity is the body mass index (BMI), which is known to correlate very well with total body as well as subcutaneous fat and, at the same time, allows a variation in lean body mass. Moreover, high BMI also correlates with blood pressure and serum lipid levels. There is an evidence that it has a considerable predictive value for obesity as also morbidity and mortality accompanying it in adult life.

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2} = \text{kg/m}^2$$

In terms of BMI, obesity in adults categorized as:

- Grade 1—25–29
- Grade 2—30–40
- Grade 3—more than 40 (moribund)

Some authorities designate BMI of 25–29 as borderline obesity or just overweight.

In children, a BMI of >22 should be considered overweight and >25 as obesity.

A superior method of defining obesity is in terms of BMI percentile. Children >2 years old with BMI >95th percentile meet the criteria for obesity and those with 85–95 percentile fall in overweight range.

Other anthropometric indices include:

- Skin-fold thickness
- Waist-hip ratio
- Weight for height.

EPIDEMIOLOGY/PREVALENCE

The rising prevalence of overweight and obese children and adolescents are one of the most alarming public health issues facing the world today. Around 50 million (20% in resource-limited world) children under 5 years of age are estimated to be overweight. Overweight and obesity are no longer limited to prosperous countries. Their prevalence is now continuously rising in low and middle income countries (particularly in urban settings) as well.

ETIOPATHOGENESIS

Exogenous (Constitutional) Obesity

This occurs as a result of excessive dietetic consumption, today's most important nutritional problem in the European countries (Box 4.9). But it is now beginning to hit the upper strata of society in the developing world as well; that is a paradox indeed. For a large segment of the population in these areas continues to live almost below the survival line. These obese children have to carry the load of a large body. This exhausts them easily, thereby further reducing their physical activity. This adds up to their obesity.

Obesity, excessive deposition of adipose tissue, results when energy expenditure is less compared to energy intake.

Besides dramatic increase in the intake of high calories, fast food as well as high calories sweetened beverages on



Fig. 4.6: Obesity. Note the characteristic facies.

top of regular diet by children, lack of physical activity is the major factor involved in obesity. Excessive involvement in multimedia, television, videogame, internet, etc. is engaging the child in a sedentary lifestyle.

Endogenous Obesity

This is associated with genetic or chromosomal syndromes, endocrinal conditions, hypothalamic causes and intake of certain drugs.

Physiological Obesity

This occurs in early adolescence and is frequent among girls in particular. It is temporary and regresses after adolescence.

CLINICAL FEATURES

Exogenous Obesity

Manifestation in a child with exogenous obesity include:

- Fat deposition is generalized (Fig. 4.6)
- External genitalia, hands and feet appear rather small,
- Knock-knee deformity (genu valgus); occasionally, slipped femoral epiphysis may also be there
- Development of pubic hair at a younger age than usual
- Irregular or absent menstrual periods
- High blood pressure
- Emotional problems. Apparently, they may seem *happy go lucky type*. But, as a matter of fact, they suffer from loneliness and profound psychological trauma.

Endogenous Obesity

Manifestations in endogenous obesity depend on the underlying condition (Figs 4.7A and B to 4.9). In Cushing syndrome, for example, obesity is typically central with involvement of upper trunk and face.

Table 4.5 lists the main differentiating clinical features between exogenous and endogenous obesity.

Somatic Types

- **General:** Excessive fat deposition is generalized.
- **Android (apple-shaped):** Waist/hip ratio 8 or less.

Box 4.9 Etiology of obesity

Exogenous

- Constitutional
- Overeating (energy intake exceeding expenditure)
- Poor energy expenditure
- Fat cell hyperplasia.

Endogenous

- **Genetic/chromosomal syndromes:** Laurence-Moon-Biedl syndrome, Turner syndrome, Prader-Willi syndrome
- **Endocrinal:** Hypothyroidism, Cushing syndrome, hypogonadotropic hypogonadism, pseudohypoparathyroidism (Albright syndrome), polycystic ovaries (Stein-Leventhal syndrome)
- **Hypothalamic:** Frohlich syndrome, postencephalitic, postmeningitic
- **Deficiency:** Leptin
- **Drug-induced steroids:** Clonazepam, valproate.



Figs 4.7A and B: Laurence-Moon-Biedl syndrome. (A) Note the obesity, short stature (height 140 cm), hypogenitalism, and polydactyly in this 14-year-old boy with an IQ of 50. Fundoscopy revealed retinitis pigmentosa; (B) Besides obesity, the child had mental retardation, polydactyly, hypogenitalism and short stature.

- **Gynoid (pear-shaped):** Both trunk and hips involved.
- **Central:** Upper trunk and face predominantly involved as in Cushing syndrome. Waist/hip ratio is >8 .

DIAGNOSIS

Diagnosis is by and large clinical. In order to label a child **fatty**, the weight should be above 20% of average weight for age and body mass index above 95th percentile (30 kg/m^2). Height may be normal or little more than the average. Investigations include:

- X-rays for bone age
- Blood sugar, cholesterol, LFT and thyroid profile
- CT scan, magnetic resonance imaging (MRI)
- Genetic studies
- Urinary free cortisol and overnight dexamethasone suppression test are indicated in select cases in which serious disease is on the card.



Fig. 4.8: Prader-Willi syndrome. Note obesity, hypotonia and hypogenitalism in this mentally challenged child. The child had note-worthy hyperphagia.



Fig. 4.9: Cushing syndrome. Note the central (buffalo hump) type obesity involving primarily the upper half of the body.

Table 4.5: Salient differences in clinical features of exogenous and endogenous obesity

Feature	Exogenous obesity	Endogenous obesity
Distribution of fat	Generalized	Central
Intelligence	Normal	Usually low
Height	Either normal or somewhat tall	Usually stunted
Blood pressure	Usually normal	Normal or elevated
Bone age	Either normal or advances	Usually retarded
Endocrinal manifestations	Nothing apparent	Acne, hirsutism, menstrual disorders (amenorrhea, menorrhagia)

Figure 4.10 gives an algorithmic approach to investigations in pediatric obesity.

COMORBIDITIES/COMPLICATIONS

These include type 2 diabetes, metabolic disease, hypertension, cardiovascular disease (Table 4.6).

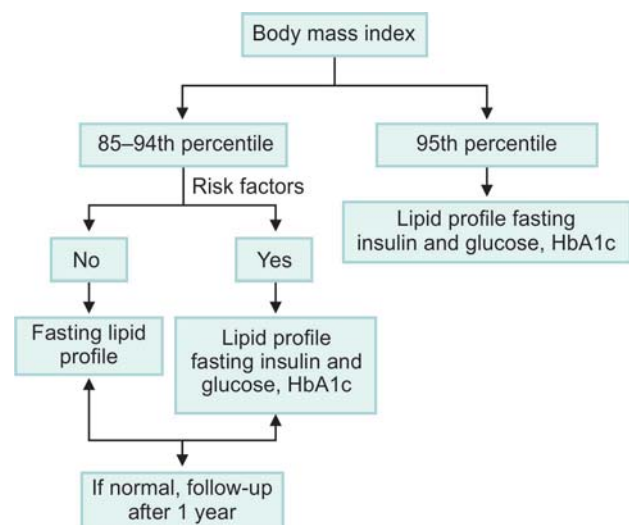


Fig. 4.10: Algorithmic approach to investigations in pediatric obesity.

Abbreviation: HbA1c, glycosylated hemoglobin.

Table 4.6: Comorbidities associated with obesity

CNS	Pseudotumor cerebri
CVS	Dyslipidemia, hypertension, coronary artery disease
Respiratory	Asthma, restrictive lung disease, obesity-hypoventilation syndrome, OSA
GIT	Gallbladder disease, non-alcoholic fatty liver disease
Endocrine	Type 2 diabetes mellitus, metabolic syndrome, polycystic ovary syndrome
Orthopedic	Genu valgus, flat feet, tibia vara (Blount disease), slipped capital femoral epiphysis, early-onset osteoarthritis
Psychologic	Anxiety, depression, low self-esteem, disordered eating, worsening school performance, social isolation

Abbreviations: CNS, central nervous system; CVS, chorionic villus sampling; GIT, gastrointestinal tract; OSA, obstructive sleep apnea.

MANAGEMENT

Dietetic Restriction

Curtailment of intake of snacks in between main meals and drastic cut-down on intake of chocolates, candies, sweets and ice cream. The traffic-light plan for various foods are given in Table 4.7.

Greater Physical Activity

Lifestyle modification in the shape of brisk walking, cycling, swimming, participation in sports and workout (exercises), and reduced television watching are helpful.

Table 4.7: The traffic-light plan

Feature	Green light food	Yellow light food	Red light food
Quality	Low-calorie, high-fiber, low-fat, nutrient-dense	Nutrient-dense, but higher in calories and fat	High in calories, sugar and fat
Type of food	Fruits, vegetables	Lean meats, dairy, starches, grains	Fatty meats, sugar, fried foods
Quantity	Unlimited	Limited	Infrequent or avoided

The results are not a matter of few days, but of months and years.

Appetite-inhibiting/suppressant agents, though often recommended in adults, are best avoided in pediatric obesity. Whereas amphetamines should be avoided, orlistat, metformin, leptin, and octreotide may be considered in select pediatric cases.

- **Orlistat**, a gastric lipase inhibitor, is the first anti-obesity agent approved for children.
- **Metformin** may be employed in insulin-resistant cases.
- **Octreotide** may prove beneficial in hypothalamic obesity.
- **Leptin**, which reduces the hypothalamic drive is indicated in leptin-deficiency obesity.

Supportive Therapy

The pediatrician must also handle the accompanying emotional overlay tactfully.

Surgery

Bariatric surgery is one of the final modes of treatment for morbid obesity (weight for height >200%, BMI >40 kg/m²). It is indicated only for adolescents and adults when other strategies have failed in comprehensive weight management program.

Laparoscopic gastric banding and gastric bypass are the popular procedures.

PREVENTION

The following measures may be of value in prevention of exogenous obesity:

- Check on obesity in adolescent girls and young women who are the potential mothers.
- Promotion of breastfeeding with introduction of semisolids after 6 months of age only.
- Promotion of healthy eating practices and avoidances of junk foods.
- Promotion of regular daily physical activity and exercise.
- Restriction of television viewing to <2 hours daily.
- Identification of obese children and encouraging them to cut down weight via acceptable means, including behavioral modifications.
- Obesity should be classified as a disease.

CRANIOSYNOSTOSIS

(Craniostenosis)

DEFINITION

Craniostenosis is defined as the premature closure of one or more of the skull sutures, leading to interference with the proper skull as well as brain growth. Since the stiff skull vault does not allow the brain to grow, a kind of situation resembling raised intracranial tension may result. Underdeveloped sinuses are a common accompaniment. Incidence is 1 in 2000 infants.

78 ETIOPATHOLOGY

Etiologically, it may well be:

- A genetic disorder occurring in association with genetic syndromes.
- Secondary to warfarin use during pregnancy.
- Without any obvious cause.

Skull growth gets restricted perpendicular to the involved suture. However, as a compensatory mechanism, excessive skull growth occurs parallel to the involved suture, resulting in a skull deformity varying with the affected suture. This facilitates accommodating the brain growth to some extent.

In addition to the primary craniosynostosis (resulting from abnormal development of skull per se), failure of brain growth, maturation and expansion may cause secondary craniosynostosis.

CLASSIFICATION

Depending on the suture or sutures involved in the following cranial deformities may result:

Scaphocephaly (Dolichocephaly)

Here, the sagittal suture is fused. As a result, skull grows anteroposteriorly and thus assumes an elongated appearance resembling a boat (Figs 4.11A and B). Hence, the name, scaphocephaly which is the most common type of craniosynostosis, accounting for around one-half of the cases.



A



B

Figs 4.11A and B: Scaphocephaly. (A) Note the boat-shaped head with significant increase in anteroposterior diameter; (B) Note the boat-shaped head as a result of premature fusion of sagittal suture.



Fig. 4.12: Brachycephaly. Note the side-to-side wide skull (just opposite of scaphocephaly in which skull is longish anteroposteriorly) with flattened front and occiput.

Brachycephaly

It is the anteroposteriorly flattened and side-to-side widened skull (Fig. 4.12) which may be seen as such or in association with plagiocephaly (asymmetrical skull). Two types are—(1) frontal and (2) cephalic. Typically, cephalic brachycephalic is seen in Down's syndrome.

Oxycephaly (Acrocephaly, Turricephaly, Tower Head/Skull)

This means fusion of multiple sutures. Coronal suture usually along with lambdoid sutures are invariably affected. The characteristic appearance is an abnormally high (tower-shaped) skull with a steep ascent of frontal and parietal areas. Underdeveloped sinuses, shallow orbits and raised intracranial pressure (ICP) are also present (Figs 4.13A and B).

Plagiocephaly

Asymmetrical fusion of suture(s), usually right-sided, leading to an asymmetrical skull with flattened occiput and bulging of the ipsilateral forehead (Fig. 4.14). When bilateral, head is



A



B

Figs 4.13A and B: Oxycephaly/acrocephaly. Also termed tower skull, it results from premature closure of coronal sutures, frequently along with lambdoid sutures and often with multiple sutures.



Fig. 4.14: Plagiocephaly. Asymmetrical skull due to asymmetrical fusion of sutures.

brachiocephalic with displacement of ears downward and anteriorly.

Trigonocephaly

It is the triangular skull secondary to premature fusion of the metopic sutures. It is characterized by a keel-shaped head that is narrow anteriorly and wide posteriorly, pointed small forehead with midline ridge, up-slanting of palpebral fissures of eyes (Mongoloid slant) and hypotelorism (Fig. 4.15). As a rule, it coexists with 19bp chromosome abnormality.

CLINICAL FEATURES

- Symptomatic subjects have manifestations secondary to high intracranial tension. These include headache, vomiting, proptosis, squint, convulsions, hyperreflexia, hypertonia and mental retardation.
- Physical examination reveals typical appearance of head and, frequently of face. Concerned sutures are united and the fontanels closed. The signs of neurological deficit may be present.
- Such anomalies as syndactyly, proptosis, hypertelorism, etc. are common accompaniments.



Fig. 4.15: Trigonocephaly. Triangular skull due to fusion of metopic sutures. Note hypotelorism.

- Association as a component of some syndromes is frequent (Box 4.10).

DIAGNOSIS

Most cases are recognized clinically. In doubtful cases, cephalic index may be of help, especially in differentiating scaphocephaly from brachycephaly.

Box 4.10

Craniosynostosis as a component of some syndromes

- **Crouzon syndrome (craniofacial dysostosis):** Brachycephaly or oxycephaly, beaked nose, proptosis and hypertelorism (Figs 4.16A and B). It is inherited as autosomal dominant trait.
- **Apert syndrome:** Premature fusion of multiple sutures, usually oxycephaly, is accompanied by syndactyly (invariably involving both fingers and toes). Compared to Crouzon syndrome, proptosis is much less (Fig. 4.17). It may be sporadic or with autosomal dominant inheritance.
- **Carpenter syndrome:** Acrocephaly, syndactyly in the hands and feet, and mental retardation are major features. Some cases may have congenital heart disease, corneal opacities, genu valgus and coxa vara. The syndrome has autosomal recessive inheritance.
- **Chortzen syndrome:** Plagiocephaly, asymmetry of face with ptosis of eyelids, syndactyly of second and third fingers, shortened fingers, etc. It is inherited as an autosomal dominant trait.
- **Pfeiffer syndrome:** Turricephaly is accompanied by wide spaced prominent eyes, short and broad thumb and great toes and partial soft-tissue syndactyly.
- **Clotzen syndrome:** Plagiocephaly, facial asymmetry, ptosis, soft tissue syndactyly (second and third toes) and shortened fingers. This is an autosomal dominant condition.



Figs 4.16A and B: Crouzon's syndrome. Note the oxycephalic head, marked proptosis, beaking of the nose and hypoplastic maxilla.



Fig. 4.17: Apert syndrome. Note the proptosis. Additionally, the child had craniosynostosis (oxycephaly) and syndactyly.

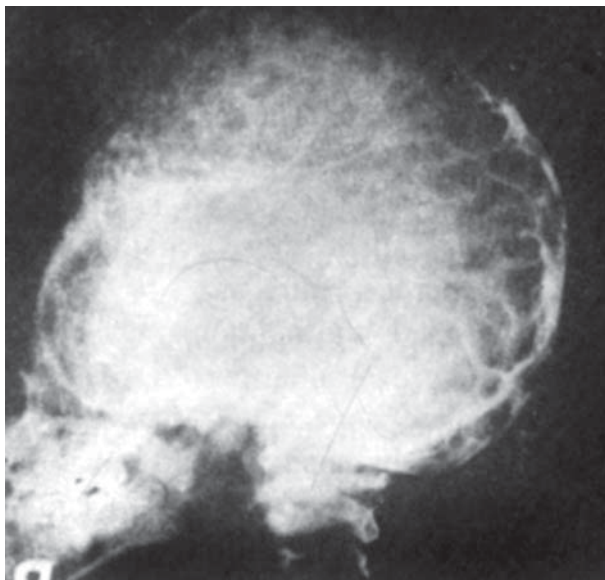


Fig. 4.18: Skull X-ray in craniosynostosis. Note the oxycephalic skull with silver/copper-beaten appearance secondary to raised ICP.

$$\text{Cephalic index} = \frac{\text{Maximum cranial width}}{\text{Maximum cranial length}} \times 100$$

In normal skulls, cephalic index varies between 70–80. An index <70 points to scaphocephaly and >80 to brachycephaly. In plagiocephaly in which shape of head is asymmetrical, it is not helpful.

Following clinical suspicion of craniosynostosis, X-ray of skull is needed to confirm the diagnosis and determining the exact sutures having premature fusion. It may also give evidence of increased ICP in the form of silver/copper beaten appearance (Fig. 4.18).

COMORBIDITIES/COMPLICATIONS

- Increased intracranial pressure (ICP)—hydrocephalus, papilledema, optic atrophy.
- Associated deviated nasal septum (DNS), choanal atresia—respiratory problems
- Deafness
- Speech problems.

TREATMENT

Surgical intervention, including craniectomy for increased ICP and surgical correction may yield the good outcome.

MICROCEPHALY

DEFINITION

It is defined as the head circumference (occipitofrontal circumference) less by more than 2–3 SD of the mean for age, sex and gestation.

At <2 SD level, a good number of children are likely to be intellectually normal. At <3 SD, nearly all are likely to be intellectually retarded because of genetic or chromosomal cause.

Box 4.11 Etiology of microcephaly

- Benign familial
- **Congenital infections:** TORCH, STORCH,
- **Acquired infections:** Meningitis, encephalitis,
- **Teratogens:** Antiepileptic's, antimalignant drugs, radiation, alcohol, tobacco, heroin, cocaine,
- **Perinatal insult:** Hypoglycemia's, HIE,
- **Metabolic disorders:** Maternal diabetes mellitus, PKU,
- **Endocrine disorders:** Hypothyroidism, hypopituitarism, adrenal insufficiency,
- **Structural defects:** NTDs,
- **Syndromal:** Trisomy 13, 18 and 21.

Abbreviations: TORCH, (T)oxoplasmosis, (O)ther agents, (R)ubella (also known as German measles), (C)ytomegalovirus, and (H)erpes simplex; STORCH, (S)yphilis, (T)oxoplasmosis, (R)ubella, (C)ytomegalovirus and (H)erpesvirus; PKU, phenylketonuria; NTDs, neural tube defects; HIE, hypoxic-ischemic encephalopathy.

TYPES

Primary Microcephaly

Reduced brain size as a result of reduced generations of neurons in the course of neural development and migration in intrauterine life.

Secondary Microcephaly

Reduced brain size as a result of insult to a previously normal brain, e.g. craniosynostosis in which brain growth gets retarded because of the restrictive effect of premature union of the sutures.

ETIOLOGY

Various causes of microcephaly are listed in Box 4.11.

CLINICAL FEATURES

In addition to small size of the head (Fig. 4.19), manifestation depends on the etiologic condition. IQ may be low in



Fig. 4.19: Microcephaly: Note remarkably small head (occipitofrontal circumference 44 cm at 8 years) in a child with primary microcephaly with mental retardation.

most case of pathological microcephaly, where the head size is $<3SD$.

DIAGNOSTIC EVALUATION

A good physical examination, including measurement of head circumference of parents is important. Abnormal shape of the head with premature closure of sutures evidenced by the ridge at the suture line points to craniosynostosis. Investigations include neuroimaging.

TREATMENT

It depends on the underlying cause.

PROGNOSIS

It is better in primary than in secondary microcephaly.

MACROCEPHALY

DEFINITION

It is defined as an occipitofrontal circumference (OFC) more than 2 SD above the mean for age, sex and gestation. Most cases showing pathological macrocephaly have OFC more than 3 SD above the mean (Figs 4.20A and B).

ETIOLOGY

Important causes of macrocephaly are listed in Box 4.12. A large number of conditions varying from familial to hydrocephalus are associated with it.

CLINICAL FEATURES

Manifestations are those of the etiologic condition. For instance, in congenital hydrocephalus, there is a postnatal rapid increase in OFC, often accompanied by irritability and vomiting.

DIAGNOSTIC EVALUATION

In addition to a good clinical workup and special investigations are indicated in the following situations:

- Severe macrocephaly, i.e. OFC >3 SD of the mean.
- Serial measurements showing a rapid increase in OFC size (>2 cm/month in first half of the first year).
- Crossing of one or more major percentile lines during follow-up visits.



Fig. 4.20: Macrocephaly. Note the large OFC (40 cm at 2 weeks) in the infant with megalencephaly (aka macrencephaly). Manifestations include delayed development, corticospinal dysfunction, and seizures.

Box 4.12 Etiology of macrocephaly

- **Megalencephaly**
 - **Familial:** A benign condition with normal body size and neurodevelopment; it persists throughout life.
 - **Syndrome-associated:** Neurocutaneous syndromes (Von-Recklinghausen, tuberous sclerosis, Sturge-Weber syndrome), fragile X syndrome, Sotos syndrome (cerebral gigantism), GM₂ gangliosidosis (Tay-Sachs disease, Sandhoff disease),
 - **Leukodystrophies:** Megalencephalic leukoencephalopathy,
 - **Lysosomal storage diseases:** Gangliosidosis (Tay-Sachs disease), mucopolysaccharidosis, gangliosidosis,
- **Raised intracranial pressure (ICP):** Hydrocephalus, hypo/hypervitaminosis A, pseudotumor cerebri, galactosemia, lead toxicity,
- **Enlarged vascular compartment:** A-V malformation, intracerebral hemorrhage (ICH) (intraventricular, subdural, epidural, sub-arachnoid),
- **Intravascular:** Bleeding into subdural, epidural, subarachnoid and intraventricular spaces,
- **Diseases related to bony compartment:** Rickets, osteogenesis imperfect, achondroplasia, osteopetrosis, cleidocranial dysostosis, hyperphosphatasia,
- **Bone marrow expansion:** Thalassemia major,
- **Intracranial space-occupying lesions (ICSOI):** Tumor, abscess, cyst.

- Investigations include cranial ultrasonography and/or CT scan.

TREATMENT

It depends on the type/cause of macrocephaly.

- In familial macrocephaly (megalencephaly) no intervention is indicated.
- Congenital hydrocephalus usually needs a shunt operation draining CSF from ventricles to peritoneal cavity (ventriculoperitoneal shunt).

Multiple Choice Questions

1. Spot the wrong observation about failure to thrive:
 - A. Failure to thrive is a descriptive rather than a diagnostic term
 - B. Slow length/height gain and/or development always accompanies FTT
 - C. Mainstay of treatment is nutritional rehabilitation
 - D. Growth retardation, developmental retardation and learning difficulties may occur in case of inappropriate management
2. Each of the following observations about short stature is correct, except:
 - A. Primordial short stature denotes short stature secondary to IUGR
 - B. In constitutional short stature, bone age is consistent with height age but less than chronological age

contd...

- C. A velocity of less than 4 cm per year between 4-5 years of age and adolescence is considered pathological
- D. Growth hormone therapy, if indicated, has got to be started after 11 years of age for attaining the optimal height
- 3. Each one of the following is a common cause of exogenous obesity, except:
 - A. Overeating (energy intake exceeding expenditure)
 - B. Poor energy expenditure
 - C. Fat cell hyperplasia
 - D. Antihypertensive drugs
- 4. Spot the wrong observation about craniosynostosis:
 - A. Manifestations in symptomatic subjects include headache, vomiting, proptosis, squint, convulsions, hyperreflexia, hypertonia and mental retardation
 - B. Brachycephaly with flattened occiput is typical of Down syndrome
 - C. Surgical intervention, including craniectomy for increased ICP and surgical correction invariably yield poor outcome
 - D. Cephalic index is the ratio between anteroposterior diameter (numerator) and side-to-side diameter (denominator) multiplied by 100
- 5. Which one is an incorrect statement?
 - A. IQ is invariably low in pathological microcephaly, where the head size is less by 3SD
 - B. In Crouzon syndrome, proptosis is much more than in Apert syndrome
 - C. Tall stature is defined as a height in excess by 3SD or above 100th percentile of the mean for age and sex
 - D. Congenital adrenal hyperplasia may cause short stature in early stage and tall stature in later stage

Answers

1. B 2. D 3. D 4. D 5. D

Clinical Problem-solving**Review 1**

A 3-year-old presents with somewhat small head, labeled by a practitioner as “microcephaly”. All gross motor, fine motor, social, and language milestones and growth and nutritional status are normal. Head circumference is 47 cm.

1. What should be the logical diagnosis?
2. Why?
3. Any other points favoring this diagnosis?

Review 2

A 6-year-old presents with a height of 100 cm (upper segment 60 cm, lower segment 40 cm), weight 20 kg, grossly delayed milestones and assessed developmental age (as per Draw-a-man test) 2 years. His calf muscles are quite bulky.

1. What type of a short stature is it keeping in mind the anthropometry?
2. What is the most likely clinical diagnosis and why?
3. What is against the diagnosis of achondroplasia?
4. Choose the two preferential investigations in this child.

Answers**Review 1**

1. Normal child with a head circumference that is on the lower side of normal range.
2. For labeling a child as “microcephaly”, head circumference needs to be less by 3SD of standard for the said age and gender. This criteria is not satisfied in this case. The child’s OFC is certainly less than the average but well within normal range.
3. The child is normal both anthropometrically and developmentally.

Review 2

1. Disproportionate short stature with infantile proportions (US/lower segment ratio 1.5:1 against the normal of 1.1:1 at 6 years).
2. Congenital hypothyroidism in view of infantile US/LS ratio, delayed milestones, and gross retardation in developmental age. Pseudohypertrophy of calf muscles is known to occur in an occasional child with hypothyroidism—the so-called “Kocher-Debre-Semelaigne (KDS)” syndrome. Overweight/obesity as seen in this child is not unusual in hypothyroidism.
3. Grossly delayed milestones and significant developmental/mental retardation are not the features of achondroplasia.
4. Skeletal X-ray (wrist and hand) for bone age and thyroid profile (T_3 , T_4 and TSH) are the essential in this case.

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DEFINITION

Development is defined as *acquisition of qualitative and quantitative skills/competencies in a social milieu*. It is a global phenomenon involved in acquisition of new motor, social, cognitive and language skills mandatory for optimal functioning of the child. Intelligence falls under its broad umbrella.

Development depends on the maturation and myelination of brain, leading to developmental milestones such as social smile, head-holding, sitting, standing and walking. It is a continuous process.

DOMAINS OF DEVELOPMENT

Development of the child is assessed in the following four major domains:

1. **Gross motor development:** It pertains to control of the child over his body and is observed in ventral suspension, supine, prone, sitting and standing positions.
2. **Fine motor and adaptive development:** It pertains to fine coordination of eyes, hand-eye, and hand-mouth, and skills for manipulation with hands.
3. **Personal/social development:** It pertains to interpersonal and social skills like social smile, mimicry, waving bye-bye, etc.
4. **Language development:** It pertains to hearing, sounds, understanding and true speech.

Over and above the aforesaid domains, **vision and hearing** is an area that is essential for child development.

NORMAL DEVELOPMENTAL MILESTONES

There are 4 major domains and 2 supportive domains of developmental milestones (Tables 5.1 and 5.2). Additional features of gross motor development in the neonatal and infancy periods are listed in Box 5.1.

Figures 5.1 to 5.17 are the illustrations for some of the important developmental milestones. Table 5.3 lists the milestones in respect of special skills.

PRINCIPLES OF DEVELOPMENT**(Laws of Development, Rules of Development)**

The development follows certain principles (Box 5.2).

VARIOUS FACTORS**INFLUENCING DEVELOPMENT**

A multitude of prenatal, neonatal and postnatal interactive factors exert influence on development. The effect is most critical during infancy and early childhood.

Table 5.1: Four major domains of developmental milestones

Milestone	Age
Gross motor	
Head/neck holding	3 months
Rolling over	5 months
Sitting (with support)	5–6 months
Sitting (without support)	7–8 months
Standing (with support)	9 months
Walking with support	10 months
Crawling/creeping	11–12 months
Standing (without support)	12 months
Walking (without support)	13 months
Running (somewhat stiff)	18 months
Running (comfortably)	24 months
Climbing upstairs (up) 1 steps at a time	18 months
Climbing stairs (down) 1 steps at a time	2 years
Climbing stairs (up) 2 steps at a time	3 years
Climbing stairs (down) 2 steps at a time	4 years
Riding tricycle	3 years
Hopping on one foot	4 years
Skipping	5 years
Fine motor	
Grasping a rattle (when placed in hand)	4 months
Reaching out for a bright object (intentional reaching) and grasps it with both hands (bilateral grasp/reach)	4–5 months
Reaching out for bright object with one hand (unilateral grasp/reach)	6 months
Transferring object from one hand to the other hand	6–7 months
Holding an object with crude grasp from palm (palmar grasp)	7 months
Holding a small object between index finger and thumb (pincer grasp which is first immature and then becomes mature)	9–12 months
Social/Adaptive/Personal	
Social smile	6–8 weeks
Recognition of mother	3 months
Stranger anxiety	6 months
Smiling at mirror image	6 months
Waving bye-bye	9 months
Playing a simple ball game	1 year
Copying parents/caretaker	18 months
Asking for food, toy, toilet	2 years
Knowing gender and name	3 years

contd...

contd...

Milestone	Age
Participating in group play	4 years
Going to toilet alone	4 years
Assisting mother in households	5 years
Dressing and undressing	5 years
Language	
Turning head to sound (rattle, ball)	1 month
Cooing	3 months
Laughing	4 months
Monosyllables (ma, pa, ba, da)	6 months
Bisyllables (mama, papa, baba, dada)	9 months
Two words with meaning	1 year
Simple sentence	2 years
Knows full name and gender	3 years
Telling a story, singing a rhyme	3–4 years
Account of recent events	4 years
Enquires about meaning of words	5 years

Table 5.2: Two supportive domains of developmental milestones

Vision	
Follows light up to 45°	Birth month
Follows light up to 90°	1 month
Follows light up to 180°	3 months
Fixating at mother	1 month
Fixating at an object	3–4 months
Reaching out for an object	6 months
Transferring an object from one hand to the other	7 months
Hearing	
Response to sounds (startle, crying, blinking)	Neonatal period
Turns head towards source	3–4 months
Turns head to one side, then downward in response to a sound below level of ears	5–6 months
Directly looks at the source of sound	10 months

**Fig. 5.1: Head holding at 3 months.** Note the good control with no lagging whatsoever.**Box 5.1**

Some important gross motor development milestones in different positions during neonatal and infancy periods

Supine and pull to sit

- If a newborn is pulled from supine position to sitting position, one can observe a complete head lag along with rounding (curvature) of the spine (back).
- In a 3-month old, head lag is minimal and spine rounding too is less.
- By 4 months of age, there is no head lag.
- By 5 months, he lifts head while in supine position.

Ventral suspension

- When a newborn is held in prone position and then lifted above the bed, he is unable to hold the head in line with trunk, i.e. the head tends to flop down.
- By 6 weeks, he can hold the head for a moment in line with trunk (horizontal position).
- By 8 weeks, he can maintain the horizontal position well enough.
- By 12 weeks, he tends to lift his head above the horizontal plane.

Prone position

- The newborn upto 2 weeks lies with high pelvis and drawn up knees.
- By 6 weeks, pelvis becomes flat and hips extended.
- By 8 weeks, face is lifted 45°.
- By 12 weeks, all three—head, face and chest lifted with weight borne on forearms.
- 4–6 month, he can rollover.
- By 8 months, he can crawl with abdomen on ground.
- By 10 months, he can creep with weight on knees and hands and abdomen off the ground.

**Fig. 5.2: Rolling over to side from prone position at 5–6 months.****Fig. 5.3: Hand regard.** Enjoying playing with own body parts at 3–5 months.



Fig. 5.4: Weight on extended arms, trunk quite lifted at 6 months.



Fig. 5.7: Crawling (hand and knee) at 9–10 months.



Fig. 5.5: Sitting with support at 6–7 months. Note that though the weight is on hands, the back is yet not straight.



Fig. 5.8: Standing with support (holding on to something like furniture) at 9 months.



Fig. 5.6: Sitting comfortably (without any support) at 7–8 months. Note the straight back.



Fig. 5.9: Walking with support (holding on to something like furniture) at 9–10 months.



Fig. 5.10: Enjoying own image in mirror at 10 months.



Fig. 5.13: Pincer grasp mature at 11–12 months. Note that good grasp between thumb and index finger without support from rest of the fingers.



Fig. 5.11: Standing without support at 11–12 months.



Fig. 5.14: Pincer grasp (immature) at 9 months.



Fig. 5.12: Walking without support at 12–13 months.



Fig. 5.15: Climbing stairs (up) a single step at a time at 18 months. Double step is learnt at around 3 years.



Fig. 5.16: Climbing stairs (down) a single step at a time at 24 months. Double step climbing down is learnt around 4 years.



Fig. 5.17: Tricycle riding at three years.

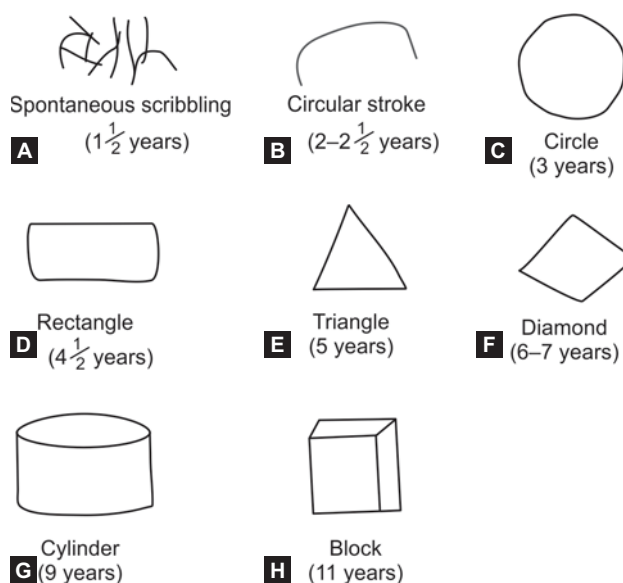
Table 5.3: Special skills

Drawing skills (Figs 5.18A to H)	
Imitates scribbling	15 months
Scribbles spontaneously	18 months
Draws a circular stroke	2–2½ year
Copies a circle	3 years
Copies a cross	4 years
Copies a rectangle	4½ years
Copies a triangle	5 years
Copies a diamond	6–7 years
Block skills (Figs 5.19A to G)	
Makes a tower of 2 blocks	15 months
Makes a tower of 3 blocks	18 months
Makes a tower of 5 or 6 blocks	2 years

contd...

contd...

Makes a train	
• Plain	2 years
• With rattle	2½ years
Makes a tower of 9 blocks	3 years
Makes a bridge	3 years
Makes a gate	4 years
Makes steps	6 years
Dressing skills	
Pulls off socks, cap, etc.	1 year
Unzips	1½ years
Undresses fully	2 years
Undresses and dresses fully	3 years
Ties shoe laces	4–5 years



Figs 5.18A to H: Drawing skills. Starting from spontaneous scribbling with a pencil, the child slowly progresses to copying a triangle at 5 years, a diamond at 6–7 years, a cylinder at 9 years and a cube at 11 years.

Overall developmental status of a child is the outcome of interplay of risk factors and protective factors.

Adverse Factors

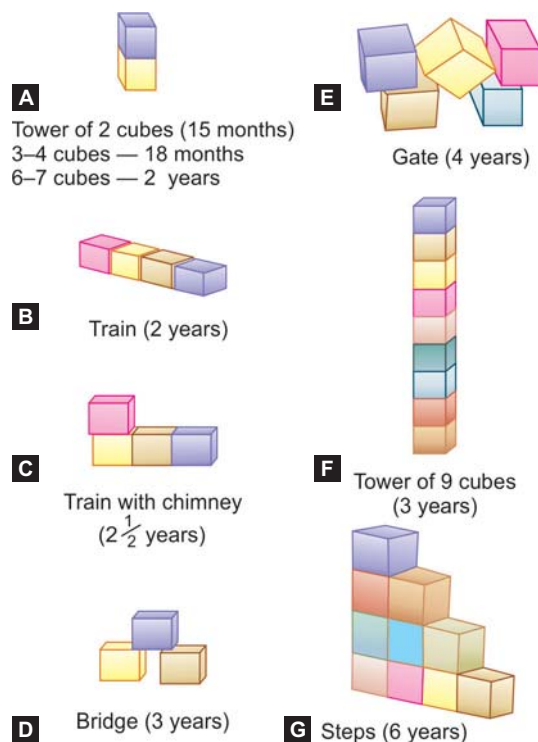
Prenatal Factors

Genetic Factors

Chromosomal disorders (Down syndrome, Turner syndrome), single gene disorders (lissencephaly), X-linked intellectual disability (Fragile X, other mutations) and inborn errors of metabolism (IEMs) such as phenylketonuria (PKU) are well known to cause developmental delay and disability.

Maternal Factors

- **Maternal nutrition:** Maternal malnutrition (including micronutrient deficiencies, especially iron and iodine) contributes to low birth weight (including IUGR) and development of the baby.



Figs 5.19A to G: Application of cubes (blocks) for testing fine motor development.

Box 5.2 Important principles of development

- **Continuous process:** Development is essentially a continuous process that takes off in utero, undergoes a developmental stages and ends at maturity.
 - **Cephalocaudal progression:** Beginning in intrauterine life, development proceeds through different phases in a standard sequence—cephalocaudal until maturity.
 - **Set sequence:** Sequence of attainment of developmental milestones remains by and large same though the time and manner of their attainment may vary within a range. For instance, head-holding, sitting, standing and walking occur in same sequence in all children. Yet, one child may learn to sit at 7 months while other at 8 or 9 months.
 - **Functional maturity of nervous system gateway to skill development:** Functional maturity of the nervous system (supported by stimulation, inputs by parents and practice) is essential for developing optimal skills. Else, skills may remain dormant to a considerable extent in spite of good maturation of the nervous system.
 - **Loss of primitive reflexes and milestones:** There are some primitive reflexes (e.g. palmar grasp reflex, asymmetric tonic reflex) that need to be lost before relevant milestones are attained. Palmar grasp reflex must disappear before development of voluntary grasp. Likewise, asymmetric tonic reflex need to be lost before the infant learns to turnover.
 - **Changeover from mass activity to organized activity:** As development proceeds, the disorganized mass activity that is conspicuously initially given place in an organized, specific and willful action. The site of a colorful, bright object prompts an infant (say 4-month-old) to respond in a disorganized manner—moving extremities with excitement and loud noise. The response in a toddler to such an object is in an organized manner. He is likely to be asking for it and throwing a smile without noise and movements of extremities.
- **Maternal medication:** Maternal substance abuse (including smoking and alcohol), use of automated external defibrillator (AEDs), antipsychotic drugs and exposure to

environmental toxins (lead, mercury, arsenic, pesticides) has adverse effect on development of the infant. **89**

- **Maternal disease:** Such diseases as hypertension, cardiovascular disease, diabetes, obesity, hypothyroidism, undernutrition and fetoplacental insufficiency, infections (TORCH/STORCH), chorioamnionitis from exposure to free radicals and oxidants may impact fetal brain development and its consequences.

Neonatal Risk Factors

Intrauterine growth restriction (IUGR), usually secondary to maternal malnutrition, infections and diseases, has considerable effect on neurocognitive development—both short-term and long-term.

Prematurity predisposes to such risks as hypoglycemia, hypobilirubinemia, hypoxia, intracranial hemorrhage (ICH) and white matter injury, resulting in developmental disability. The risk is much more <32 weeks than <37 weeks gestation.

Asphyxia and hypoxic-ischemic encephalopathy (HIE), occurring in some 2% of all birth, causes neurocognitive impairment in nearly half of the survivors.

Postneonatal Factors

- Erratic infant and young child nutrition resulting in PEM and micronutrient deficiencies (IDA, goiter, congenital hypothyroidism) are known to have significant cognitive dysfunctions.
- Infectious diseases may adversely affect the neurodevelopment of the child.
- Environmental toxins such as lead, mercury, arsenic, and pesticides may pass onto the child via breastfeeds, water, foodstuffs, etc. and exert deleterious effects on neurodevelopment.
- **Central nervous system (CNS)** insult from acquired conditions such as encephalitis, meningitis, cerebral malaria, hepatic encephalopathy, head injury, drowning, etc. in early years of life may cause permanent neurodevelopmental impairment.
- Associated impairments such as hearing loss or blindness (often responsive to intervention) may impact the sensory inputs and cause delayed milestones.

Psychosocial Factors

Such psychosocial factors as poor quality of parenting, lack of stimulation, maltreatment/CAN, maternal depression, poverty, violence (both domestic and community) and Institution placement leave a considerable adverse effect on neurodevelopment, especially cognition.

Protective Factors

Breastfeeding

The breastfeeding has a protective and promotive influence on neurodevelopment of the child stands well established.

Well Informed Educated Parents

Well informed educated parents, the mothers in particular are successful in imparting higher cognitive abilities to their children.

90 Parental Positive Attitudes

Parental positive attitudes providing cognitive stimulation, emotional warmth and responsiveness are associated with high level of neurodevelopment.

ASSESSMENT OF DEVELOPMENT

Today, thanks to high level of tertiary neonatal care, a good proportion of low birth weight including very low birth weight (VLBW) and extremely low birth weight (ELBW) and other high-risk infants survive. They stand significant risk of suffering from developmental delay and disability. A good follow-up paves the way for identification of developmental delay and early interventions to improve their quality of life (QOL).

Two phases of assessment of development are:

1. Developmental screening
2. Definitive tests to define impairment in sphere and degree.

Developmental Screening

Developmental screening is a brief testing procedure designed to identify children who should receive more intensive diagnosis or assessment. It is essential for detecting abnormal developmental delay which is expected in some 10% children.

Types

- **Informal screening:** It aims to correctly identify children with subtle developmental delays through informal screening methods such as observations during routine pediatric checkup and obtaining information from parents about their concerns concerning child's developmental milestones at various ages (Box 5.3).
- **Routine formal screening:** It consists in systematic developmental screening of all children with the help of standardized screening instruments. This approach is neither feasible nor cost effective.
- **Focused screening:** It comprises of developmental screening in the following situations:
 - Children whose parents and/or teachers suspect developmental problems
 - High-risk neonates (for developmental delay) as per Box 5.4.

Guidelines

The guidelines for developmental screening are summarized in Box 5.5.

Various Tests Employed

The most widely used screening for detecting developmental delays in infancy and preschool years are the Denver Developmental Screening Test (DDST). For older children, 3 to 15 years, one may use the development charts. Remember, assessment of development must not be confused with assessment of general intelligence using

Box 5.3

Role of history and physical examination in initial development screening

History

- **Developmental milestones:** Time of acquisition, delay and regression if any. While assessing a milestone, not just the average age of acquisition, but also the upper limit of normalcy for milestone in reference should be borne in mind before labeling it as delayed.
- **Risk factors:** Any adverse factors that could delay or regress development.
- **Developmental age:** Assessed developmental age with developmental quotient.

Physical examination

- Head circumference
- Any dysmorphism
- Stigmata of TORCH/TORCH infections
- Evidence of known conditions with developmental/intellectual disability, i.e. congenital hypothyroidism, Down's syndrome, Turner's syndrome, Fragile-X syndrome, phenylketonuria, etc.
- Any hearing or vision loss
- Vocal responses
- Fine motor skills
- Social responses, alertness, attentiveness, concentration, etc.
- Observed developmental delay
- Development quotient for <5 years and intelligence quotient for five years and beyond.
 - In case of preterm babies, it is important to take into account the corrected age* rather than postnatal age till two years of age.
 - Upper limit of age for achieving different milestones must be borne in mind before labeling a milestone as delayed.
 - Occasionally, there may be variation (dissociation) in achieving milestones in individual fields, e.g. a 2-year-old with all milestones normal may have speech problem because of hearing loss.
 - A single feature should not be considered sufficient for labeling developmental delay.
 - An attempt should be made to determine the cause of delay.

* Corrected age = Postnatal age in weeks – number of weeks by which the child was born preterm. Example. A neonate born at 36 weeks of gestation is preterm by 4 weeks. His corrected age at postnatal 6 weeks of age is 6–4 = 2 weeks.

Box 5.4

High-risk neonates (for developmental delay) in need of focused developmental screening

- Very LBW infants
- Neurologic conditions: IVH (Grades 3 & 4), HIE, Apgar score 0–3 at 0, 15 and 20 minutes, periventricular leukomalacia, meningitis, persistent seizures, apnea beyond term
- Hyperbilirubinemia
- Septicemia.

Once preliminary history-taking and examination has been carried out, it becomes clear whether the child indeed suffers from developmental delay. It needs to be differentiated if it is indeed delay or regression. Furthermore, it should be ascertained if the developmental delay is global or dissociative (limited to just one of more domains). It is advisable to calculate the developmental quotient (wide infra).

Abbreviations: LBW, low birth weight; IVH, intraventricular hemorrhage; HIE, hypoxic-ischemic encephalopathy.

such tests as Stanford-Binet intelligence scale, Wechsler intelligence scale and Goodenough draw a man test.

Denver Developmental Screening Test

Developed in 1967, Denver developmental screening test (DDST) assesses development of infants and preschool children (usually upto 3 years) in 4 vital areas namely **gross**

Box 5.5 Guidelines for developmental screening

- Screening instrument should be
 - Reliable
 - Culturally relevant
 - Used only for specified purpose.
 - Multiple sources of information should be used.
 - Developmental screening should be done only by trained personnel.
 - Screening should be on a recurrent and periodic basis
 - Family members should be part of the screening process.
- In a nutshell, the pediatrician should rely on a combination of clinical judgment, based on history, physical examination and office observations, parental concerns, and formal screening test to identify children with developmental disability.

motor, fine motor adaptive, language, and personal social behavior. There are 105 items, some of which are indeed difficult to administer. Moreover, it is inappropriate for children with mothers who are not having enough education and has fewer items related to language. A short DDST is available, but it has got to be followed by the full DDST subsequently for dependable results.

Denver II (Modified DDST): Recently, major revision, modification and standardization of the DDST have occurred in the form of Denver II which has 125 items instead of 105. The major differences from the original test are:

- An 86% increase in language items
- Two articulation items
- A new-category of item interpretation to identify milder delays
- Behavior rating scale
- New training materials
- Higher inter-rater and test-retest reliability
- Designation of caution items
- Identification of items for which there is a clinically significant difference between the norms of one or more subgroups and the composite norms of the total samples.

Denver II has following plus points over DDST:

- Availability of Denver II screening manual
- Availability of Denver II technical manual
- Availability of a video instructional program and proficiency test.

Note that it is only a screening test for identifying children who are not performing as their agemates, irrespective of the reason(s). It does not measure intelligence or developmental quotient.

Attempts are being made to produce a short (abbreviated) Denver-II needing just 5 minutes for assessment.

Baroda Developmental Screening Test

Also called Phatak's DST, the **Baroda screening** test has 25 test items listed according to child's age. It is primarily developed for use of the child psychologists rather than pediatricians. In order to have a suitable developmental screening test for Indian children, it was adopted from Bayley development scale by Phatak from Baroda. The test is relevant for age 0–30 months. Domains evaluated are gross motor, fine motor and cognitive. Administrative time is 10 minutes. Sensitivity is 0.66–0.93; specificity is 0.77–0.94.

Table 5.4: Trivandrum development screening chart

Test items	3rd percentile	97th percentile
Social simile	0.1	2.7
Eyes follow pen/pencil	1.1	3.9
Holds head steady	1.1	3.8
Rolls from back to stomach	2.7	10.0
Turns head to sound of bell/rattle	3.0	5.8
Transfers objects hand to hand	4.1	7.0
Raises self to sitting position	5.8	11.0
Standing up by furniture	6.3	11.0
Fine prehension pellet	6.7	10.9
Pat-a-cake	6.7	12.7
Walk with help	7.7	13.0
Throws ball	9.5	16.7
Walk ball	9.9	17.7
Walk alone	11.2	19.1
Walks back wards	12.2	19.5
Walks upstairs with help	12.2	24.4
Points to parts of a doll (3 parts)	15.3	24.3

Trivandrum Developmental Screening Test

This test is based on Baroda norms and has 17 test items (Table 5.4). It is relevant for age 0–2 years. Domains evaluated are gross motor, fine motor and cognitive. Administrative time is 5 minutes. Validity and specificity are 0.67 and 0.79, respectively.

Goodenough Draw-a-Man Test

(Goodenough-Harris Drawing Test, Goodenough-Harris Draw a Person Test)

First developed by Florence Goodenough in 1926 and later revised by B. Harris, this simple test is a paper-pencil test meant for 3–15 year age group. The child scores as many points as the number of items he includes in his drawing. For every 4 points he is awarded one year that is added to the basal age (3 years).

For example, the 8-year-old who includes 16 items in the drawing attains a score of 4 years (Fig. 5.20).

His mental age = 3 + 4 = 7 years.

$$\text{Hence, IQ} = \frac{\text{Mental age}}{\text{Chronologic age}} \times 100 = \frac{7}{8} \times 100 = 87$$

This test is of value as a group screening tool. It provides a quick (though somewhat rough) estimate of child's cognitive status.

Definitive Development Assessment Tests

Once screening test(s) have demonstrated an impairment, definitive determination of degree and sphere may be done by more sophisticated tests such as:

- Bayley scale for infant development II,
- Wechsler intelligence scale for children IV,
- Stanford-Binet intelligence scale, 5th ed,

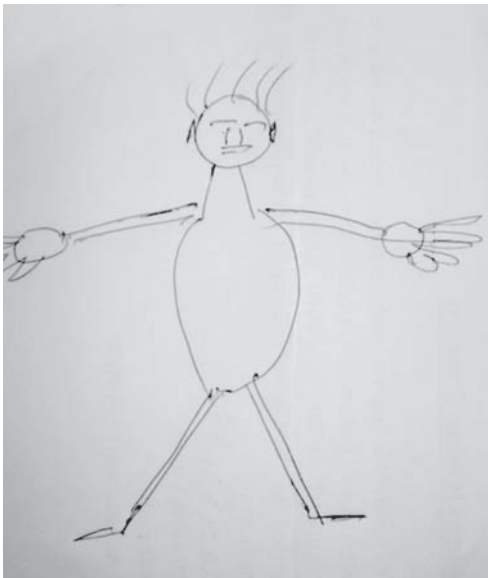


Fig. 5.20: Draw-a-man test. The figure was drawn by an 8-year-old girl. The child has drawn 12 items, thereby scoring 12 point. Since each 4 points are taken as one year, she scores 3 years for that. Thus, this girl's developmental age = base age of 3 years + another 3 years (based on performance in drawing the figure of man) = 6 years.

- Vineland social maturity scale/adaptive behavior scale II,
- Gessel's DST,
- Woodside DST,
- Developmental profile (DP-II),

- Cognitive adaptive test (CAT)/clinical linguistic auditory milestone scale (CLAMS),
- Early language milestone scale (ELM).

These are carried out by a trained developmental psychologist rather than a pediatrician.

Figure 5.21 gives an algorithmic approach for evaluation of developmental delay.

Once identification of developmental delay has been made, early treatment and intervention (say application of stimulation modalities) must begin before it affects the functioning of the child and the family.

The following formula is employed for calculating development quotient (DQ):

$$DQ = \frac{\text{Development age}}{\text{Chronologic age}} \times 100$$

Generally speaking, if DQ is <70, the child is likely to suffer from intellectual disability (mental retardation). A child with DQ between 70 and 84 is likely to suffer from learning disorders.

Intelligence Quotient (IQ)

The term, intelligence, means *the cognitive ability to acquire, learn, store and selectively reproduce skills and knowledge*. Though having variable definition, it is the particular component of development that pertains to cognitive and adaptive behavior. In other words, it is the global ability to apply knowledge to manipulate

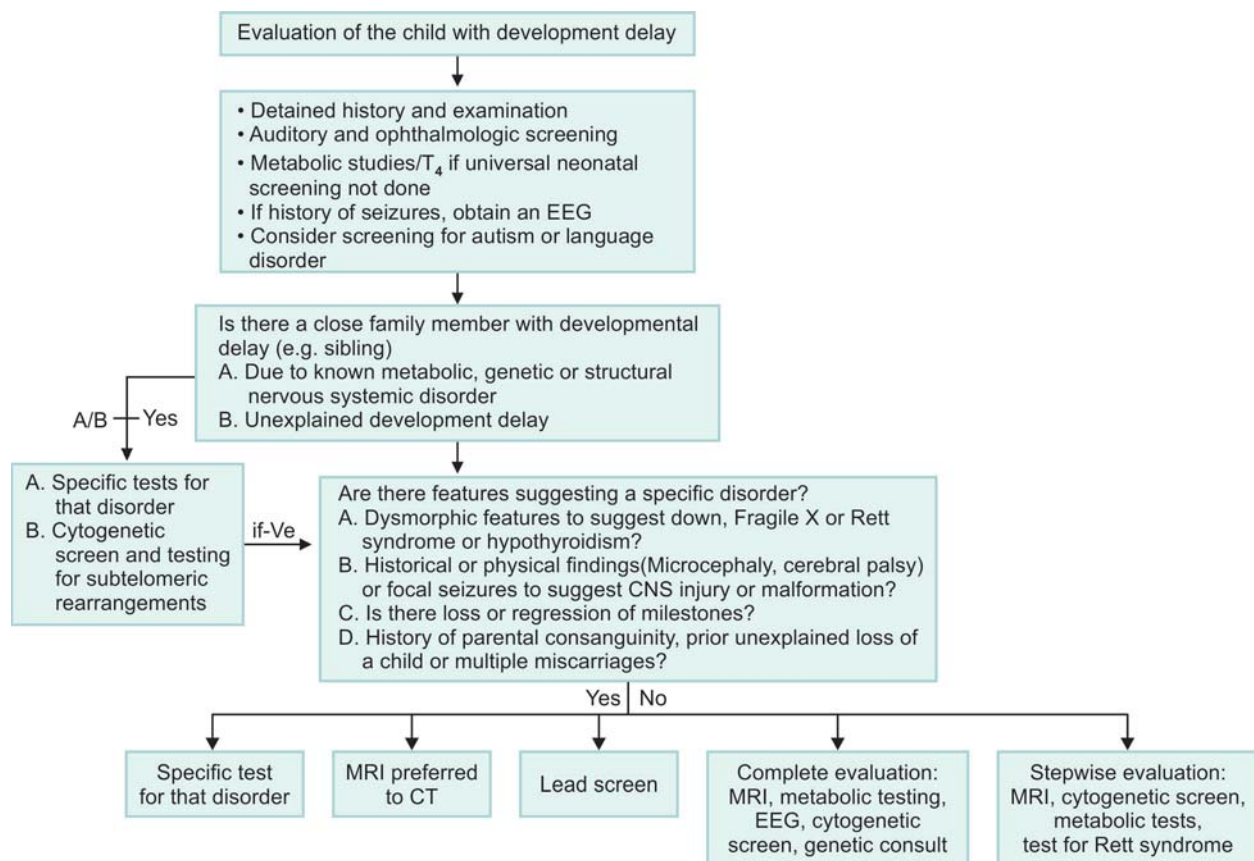


Fig. 5.21: An algorithmic approach for evaluation of developmental delay.

Abbreviations: MRI, magnetic resonance imaging; CT, computed tomography; EEG, electroencephalography; CNS, central nervous system.

Table 5.5: Grading of IQ

Grade	Range	Special comment/action required
Normal	85–115	
Borderline	70–85	Vulnerable to educational problems
Mild	50–70	Educable usually via special classes (mainstreaming)
Moderate	35–50	Trainable (workshop setting)
Severe	20–35	Trainable (self-care skills)
Profound	<20	Custodial care

environment, think rationally and deal effectively in a given situation.

IQ, a measure of cognitive ability, is an average of various mental functions that are tested. It is a score derived from one of several standardized tests designed for its assessment.

The term was coined by the German psychologist, William Stern, for the German term, *intelligenz-quotient*, in 1912.

Broadly speaking, approximately two thirds of human population scores between IQ 85 and 115, and about 5% percent of the population scores above 125.

Calculation of IQ is by the following formula:

$$IQ = \frac{\text{Mental age}}{\text{Chronologic age}} \times 100$$

Table 5.5 gives the popular grading of IQ as per DSM-5. The World Health Organization (WHO) grading remains similar except that it does not include borderline mental disability (IQ 70–85).

Various tests employed for IQ assessment are listed in Box 5.7.

The application of these tests primarily comes in the domain of psychologists/psychiatrists.

Recently, a new term, *emotional intelligence*, has been proposed. This refers to the emotional health of an individual-his/her ability to balance his emotions and understand others emotions.

PROMOTION OF DEVELOPMENT

(Early Intervention Therapy)

Sensible Parenting

Knowledgeable and conscientious parents can contribute immensely to positive emotional, social and cognitive dev-

Box 5.7 Features of abnormal breathing pattern

- Stanford-Binet intelligence scale (Indian modification)
- Binet-Kamat test (Indian modification)
- Wechsler intelligence scale (Indian modification)
- Malin intelligence scale (Indian modification)
- Goodenough draw-a-man test (Indian modification)
- Tests of cognitive function.

Box 5.8

Some ways of providing stimulation as an early intervention therapy for promotion of development

- Providing age-appropriate colorful toys for manipulation and using these when child is most active and in a playful mood.
- Putting an extra effort to make the child sit, stand or walk.
- Talking to the child and stimulating him to respond by speaking.
- Encouraging child's interaction with other children.
- This stimulation can be useful in improving neurodevelopmental abilities.

elopment of the child. For instance, nothing matches the proper toilet training to the child starting at the appropriate age of the parents.

Early and Timely Stimulation

Examples of such stimulation are listed in Box 5.8.

Balanced Television-Exposure

Television viewing has become a part and parcel of life. However, parents need to regulate the quantity and quality of TV viewing by children. Generally speaking, recommended 1–2 hour/day limit should not be crossed. Parents should also ensure that only useful content is viewed. Excessive TV viewing contributes to the development of obesity as well. Also, See Chapter 8 (Pediatric-related Biostatistics).

Soft Neurological Signs and Development

By definition, the term, soft neurological signs (SNS), refer to developmental signs that are normally present during neurodevelopmental phase (infancy and first 4–6 years of life). Unlike SNS, hard neurological signs (HNS) always point to the existence of a neurological disorder such as seizures or cranial nerve involvement causing deafness or blindness.

Persistence of two or more such signs in later years should be considered abnormal neurodevelopment in the following ways:

- Impaired motor development
- Poor sensory perception
- Difficulties in sequencing of complex motor tasks
- Difficulties in brain structural abnormalities.

Cerebral palsy (CP) and attention deficit hyperactivity disorder (ADHD) are two major examples of neurological disorders in which SNS may be encountered.

Some of the examples of SNS with their significance are:

- **Failure to show right hand, ear or eye:** Laterality deficit.
- **Failure to touch thumb with index finger:** Lack of orientation in space and time.
- **Failure to tackle localization:** Special senses abnormalities.
- **Failure to dress and undress:** Fine motor incoordination, finger tapping, rapid alternate movements.

Multiple Choice Questions

1. A 3-year-old is capable of performing each of the following activities, except:
 - A. Drawing a triangle
 - B. Climbing up stairs 2 steps at a time
 - C. Speaking sentences
 - D. Knowing his name and gender
2. A 15-month-old baby can do all these except:
 - A. Draw a line with a pencil/crayon
 - B. Walk independently
 - C. Say bye bye
 - D. Climb upstairs
3. What is the most frequently employed developmental screening test?
 - A. Trivandrum developmental screening test
 - B. Denver developmental screening test
 - C. Baroda developmental screening test
 - D. Woodside scale for development
4. A child stands with support, speaks mama and has immature pincer grasp. What is his approximate developmental age?
 - A. 6 months
 - B. 9 months
 - C. 1 year
 - D. 18 months
5. Spot the wrong entry:
 - A. Handedness is usually established at 2 years of age
 - B. Tanner staging is the standard method of pubertal assessment
 - C. The first accessible milestone achieved by an infant is social smile
 - D. Mature pincer is achieved by 9–10 months of age

Answers

1. A 2. A 3. B 4. B 5. D

Clinical Problem-solving

Review 1

A 25-month-old child comfortably climbs up stairs one step at a time. He can scribble a circular line. He can also make a train out of a few cubes (blocks). However, his speech is restricted to sheer bisyllables.

1. What is his approximate developmental age in terms of motor and social milestones?
2. When is he likely to climb up stairs 2 steps at a time?
3. When is he likely to draw a triangle?
4. How to sort out the problem of delayed speech?

Review 2

A 30-month-old born preterm, was suspected to be suffering from developmental delay in social and language milestones.

1. What should be the next step?
2. Supposed the presence of developmental delay is confirmed, what should be the course of action?
3. What is the way out?

Answers

Review 1

1. Two years. Though the child on an average learns climbing up stairs one step at a time at about 18 months, comfortable climbing takes another 3–6 months. Scribbling a circular stroke and making a train out of cubes too happens around 2 years.
2. Three years
3. Five years
4. His delayed speech may well be related to hearing loss. It is, therefore, mandatory to have his appropriate checkup for deafness.

contd...

Review 2

1. A standardized developmental screening test is required to confirm the presence of developmental delay.
2. If the screening test (say, Baroda) has turned out to be abnormal, it is important to accurately define the developmental impairment and quantify it (both in degree and sphere).
3. Early stimulation in the form of such inputs as opportunities for body control, and acquisition of motor, language and psychosocial skills may be helpful to the child.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

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3. Phatak P, Dhapre M, Pandit AN, Kulkarni S. A study of Baroda development screening test of Indians. *Indian Pediatr* 1991; 28:843–849.

BOOKS/MONOGRAPHS

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn. Arlington, VA.: American Psychiatric Association 2013.
2. Gupte S. *Recent Advances in Pediatrics (Special Vol. 19: Developmental and Behavioral Pediatrics)*. New Delhi: Jaypee 2007.
3. Goodman AW. *Growth and Development: Normal and Abnormal*, 4th edn. London: Smith and Smith 2013.
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DEVELOPMENTAL DELAY

DEFINITION

If the child fails to attain the key milestones by the expected age (which is a range rather than a fixed point), he is said to suffer from **developmental delay**. The lag may well be in motor, cognitive, social, behavioral or emotional development as compared to the norms. However when delay is in all developmental areas, it is termed **global delay**.

Around 10% children are estimated to suffer from developmental delay; the incidence showing an increase with the enhanced survival of neonates at risk, especially very low birth weight (VLBW) and extremely low birth weight (ELBW) babies.

For the average ages at which various developmental milestones are attained, See Chapter 4 (Growth Disorders).

ETIOLOGY

A large number of conditions may cause developmental delay (Box 6.1). Once mental retardation is present, there is a considerable probability of global delay. Causes of global developmental delay include genetic and chromosomal disorders, e.g. Down's syndrome, Fragile X syndrome, Turner's syndrome, etc.

DIAGNOSIS

Early recognition of developmental delay by simple clinical approach is important.

Box 6.1 Causes of developmental delay

- **Bad obstetrical history:** Abortion/miscarriage
- **Maternal illnesses during intrauterine life:** Toxemias, infections (TORCH/STORCH)
- **Perinatal problems:** Obstetric complications, HIE, LBW/prematurity, multiple pregnancy, neonatal seizures, IVH, septicemia, meningitis, kernicterus
- **Nutritional factors:** Chronic PEM
- **Social factors:** Poor socioeconomic status, teenage mother, mentally retarded parent(s)
- **Organic disorders:** Genetic disorders (PKU), chromosomal aberrations (Down syndrome, Turner syndrome), blindness, deafness, post-meningitis/encephalitis sequela.

Abbreviations: TORCH, (T)oxoplasmosis, (O)ther agents, (R)ubella (C)ytomegalovirus and (H)erpes simplex; STORCH, (S)yphilis, (T)oxoplasmosis, other infections, (R)ubella, (C)ytomegalovirus infection, and (H)erpes simplex; HIE, hypoxic-ischemic encephalopathy; LBW, low birth weight; IVH, intraventricular hemorrhage; PEM, protein-energy metabolism; PKU, phenylketonuria.

A good history and detailed examination, especially identification of congenital malformations and neurologic workup, are crucial.

Some developmental disorders (say cerebral palsy) may be picked up in infancy per se. Speech disorders, hyperactivity and emotional disturbances usually need waiting for 3–4 years and learning disabilities till schooling begins.

For developmental screening, See Chapter 4 (Growth Disorders).

MANAGEMENT

The following measures of early stimulation help many infants and children to grow out of the suspected developmental delay:

- Playing with him, employing age-appropriate colorful toys for manipulation.
- Putting up efforts to make him sit, stand and walk.
- Showing him bright catchy objects.
- Talking to him; provoking him to speak.
- Encouraging him to interact with others.

SPECIFIC LEARNING DISORDER

(Dyslexia, Dysgraphia, Dyscalculia; Dyslexia spectrum; Learning disabilities)

DEFINITION

The term **learning disabilities** denotes “disorders in one or more of the basic processes involved in understanding or in using language (spoken or written) that may manifest itself in an imperfect ability to listen, speak, read, write, and spell or to do arithmetic calculations”. In other words, this is a disorder that interferes with child's ability to store, process or reproduce information.

Since these three types of learning disabilities frequently overlap and are highly interrelated, DSM-5 has revised the diagnosis into a single category—**specific learning disorder**.

Notwithstanding learning disability, child's intelligence is usually normal or even above average. Of course, there is a discrepancy between his potentials and ability on one hand and achievements on the other hand. Though the disability may be mild enough to remain undetected throughout life, it may impact child's academic and emotional development.

“The celebrities Edison, Einstein and Leonardo da Vinci (Italian painter, known for famous work, Mona Lisa) reportedly suffered from dyslexia and yet made it ‘big’ in their fields.”

PREVALENCE

Dyslexia is the most common neurobehavioral disorder with prevalence of 5–18%. Contrary to earlier observation of higher incidence in boys, both sexes appear to be equally affected.

ETIOLOGY

- Genetic predispositions appear to play an important role. First degree relatives with learning disability, prenatal cigarette exposure, lead exposure and protein-energy metabolism (PEM) are risk factors. A dyslexic parent may pass on the disorder upto half of the children. Also, half of the siblings of a dyslexic child are likely to suffer from dyslexia.
- Association with attention deficit hyperactivity disorder (ADHD) is well known, the two conditions coexisting in around one-third of cases.
- A large proportion of the children has had delayed speech and language development.
- Socioeconomic, cultural, environmental and educational factors and also other disabilities are not the primary cause.

PATHOPHYSIOLOGY

There is no organic brain lesion in most of the cases. The disorders are believed to be intrinsic to the individual and secondary to dysfunction of the brain.

CLASSIFICATION

Learning difficulties may be global (all aspects of learning are affected because of low intelligence quotient {IQ}) or specific. Here we are concerned with specific leaning difficulties, so the characteristic of dyslexia spectrum, namely:

- Reading disorder (Dyslexia)—responsible for 4/5th cases of learning difficulties.
- Disorder of written expression (Dysgraphia).
- Mathematical disorder (Dyscalculia)

These disabilities usually occur in combinations.

- **Dyslexia:** A specific language disorder of constitutional origin, it is characterized by difficulties in single word decoding as a result of insufficient phonological processing abilities. Therefore, the child has a problem in reading as well as acquiring proficiency in writing and spelling.
- **Dysgraphia:** A developmental writing disability characterized by difficulty in expressing thoughts on paper in association with a writing that is unreadable and problems in gripping and manipulating a pencil or pen.
- **Dyscalculia:** This is a mathematical disability characterized by unusual difficulty in solving arithmetic problems and grasping concepts like addition, subtraction, multiplication, division, etc. Additionally, there is poor retention and retrieval of math concepts.

Additionally, *nonverbal learning disabilities* are developmental coordination disorders of motor function,

visiospatial processing, mathematics, memory, prefrontal executive function and socioemotional cognition and behavior.

CLINICAL FEATURES

Child's performance remains behind his actual potentials though his intelligence is by and large within normal limits. This results in poor scholastic achievements and even failures. Major manifestations are:

- Difficulties in acquiring and using language:
 - Reading and writing letters in the wrong order.
 - There is directional confusion as well as confusion regarding capital and small letters.
- Difficulties in learning to speak.
- Difficulties in learning letters and their sounds.
- Difficulties in memorizing number facts.
- Difficulties in learning foreign languages.
- Difficulties in doing math operations.

DIAGNOSIS

Discrepancy between potential (ability, IQ) and achievement, resulting in underachievement, especially in reading, is the most important clue. Unexpected difficulties in reading should arouse suspicion.

- **History:** Inquiry into prenatal, perinatal or postnatal factors contributing to learning disability. Information with respect to marital disharmony, unrealistic expectations from the child, sibling rivalry, discrimination and emotional trauma should be sought.
- **Physical examination:** It should exclude any neurological deficit, hearing and visual loss.
- **Investigations:** These include screening for hearing, vision, speech and psychoeducational status.

In order to test speed, accuracy and comprehension in reading and spelling, certain special tests can be conducted. DSM-5 diagnostic criteria are listed in Box 6.2.

COMORBIDITIES

- Behavioral disruptions
- Enhanced exposure to failure and frustration
- Adverse impact on personality development
- Adverse family reactions
- Social stigma.

MANAGEMENT

Multidisciplinary Approach

A multidisciplinary approach, involving the class teacher, remedial teacher, parents, social worker, pediatrician, psychologist and, if warranted, even a psychiatrist, is important in managing the learning disability. The teaching curriculum is adjusted and specific teaching materials employed to help the child in exploring his optimal learning potential. For reading disability, the child should be taught:

- To break the spoken words into smaller units of sound,
- That letters on the page represent these sounds,
- That written words have the same number and sequence of sounds as heard in spoken words,
- Phonemic awareness.

Box 6.2 DSM-5 diagnostic criteria for specific learning disabilities

- A persistent difficulty in learning academic skills for at least 6 months despite intervention targeting the area(s) of difficulty. Many schools use an response to intervention (RTI) model of academic skill assessment and progress monitoring to determine the effectiveness of interventions. The areas of documented academic skill difficulties include:
 - Word decoding and word reading fluency
 - Reading comprehension
 - Spelling
 - Writing difficulties such as grammar, punctuation, organization, and clarity
 - Number sense, fact and calculation
 - Mathematical reasoning.
- The affected academic skills are substantially below expectations given the individual's age and result in impaired functioning in school, at work and in activities of daily living.
- Learning disabilities (LD) is readily apparent in the early years; however, it is not to be diagnosed until the onset of school years; in some individuals the disorder is not apparent until the onset of a demand for higher-level skills.
- The academic and learning difficulties occur in the absence of:
 - Intellectual disabilities
 - Visual or hearing impairments
 - Mental disorders (e.g. depression, anxiety, etc.)
 - Neurological disorders
 - Psychosocial difficulty
 - Language differences
 - Lack of access to adequate instructions.

Additional helpful measures include:

- Practice in reading stories is useful,
- Computers with spelling checker,
- Tape-recorders,
- Recorded books,
- Oral rather than written examination,
- Drug therapy for comorbidities such as emotional problems, hyperactivity and enuresis.

Special Considerations

The special consideration for these children by several education boards includes:

- Second language exemption,
- Extra time for examination,
- Provision of scribe,
- Use of calculators in the exams.

The National Institute of Open Schooling offers a wide selection of vocational and non-vocational subjects upto pre-degree level to circumvent the difficulties of these children. No paper is compulsory.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

It is defined as hyperactivity, impulsiveness and inattentiveness that are inappropriate for age. Boys suffer thrice compared to girls.

The diagnostic and statistical manual of mental disorders (DSM-5)* focuses on the continuation of attention deficit hyperactivity disorder (ADHD) manifestations in adulthood.

CLASSIFICATION

- **Class I:** Hyperactivity, impulsiveness and inattentiveness (most common).
- **Class II:** Hyperactivity and impulsiveness only.
- **Class III:** Mainly inattentiveness (uncommon).

ETIOLOGY

The cause is not precisely known though brain damage, prematurity, low birth weight, and psychosocial and genetic factors have been blamed.

An interaction between biological (genetic endowment) and psychosocial factors appears to be the cause. Of course, clinical expression is influenced by child's environments. Problems of attention and learning difficulties may well be secondary to frustration.

DIAGNOSIS

Subjects with ADHD show a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. Revised DSM-5 criteria for ADHD are listed in Box 6.3.

Box 6.3 Revised (DSM-5) criteria for ADHD

- **Inattention:** Six or more symptoms of inattention for children up to age 16, or five or more for adolescents 17 and older and adults; symptoms of inattention have been present for at least 6 months, and they are inappropriate for developmental level:
 - Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities.
 - Often has trouble holding attention on tasks or play activities.
 - Often does not seem to listen when spoken to directly.
 - Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g. loses focus, side-tracked).
 - Often has trouble organizing tasks and activities.
 - Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework).
 - Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).
 - Is often easily distracted.
 - Is often forgetful in daily activities.
- **Hyperactivity and impulsivity:** Six or more symptoms of hyperactivity-impulsivity for children upto age 16, or five or more for adolescents 17 and older and adults; symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that are disruptive and inappropriate for the person's developmental level:
 - Often fidgets with or taps hands or feet, or squirms in seat.
 - Often leaves seat in situations when remaining seated is expected.

contd...

* The Diagnostic and Statistical Manual of Mental Disorders (DSM) is the authoritative guide concerning the mental disorders. DSM has been periodically reviewed and revised since it was first published in 1952. The DSM-5 is the latest edition that has come in 2013, two decades after DSM-4. It incorporates a wealth of new research and knowledge about neurodevelopmental, behavioral, psychiatric and mental disorders.

contd...

- Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).
 - Often unable to play or take part in leisure activities quietly.
 - Is often on the go acting as if driven by a motor.
 - Often talks excessively.
 - Often blurts out an answer before a question has been completed.
 - Often has trouble waiting his/her turn.
 - Often interrupts or intrudes on others (e.g. butts into conversations or games).
- In addition, the following conditions must be met:
- Several inattentive or hyperactive-impulsive symptoms were present before age 12 years.
 - Several symptoms are present in two or more setting, (e.g. at home, school or work; with friends or relatives; in other activities).
 - There is a clear evidence that the symptoms interfere with, or reduce the quality of social, school, or work functioning.
 - The symptoms do not happen only during the course of schizophrenia or another psychotic disorder. The symptoms are not better explained by another mental disorder (e.g. mood disorder, anxiety disorder, dissociative disorder, or a personality disorder).
- Based on the types of symptoms, three kinds (presentations) of ADHD can occur:
- **Combined presentation:** If enough symptoms of both criteria inattention and hyperactivity-impulsivity were present for the past 6 months.
 - **Predominantly inattentive presentation:** If enough symptoms of inattention, but not hyperactivity-impulsivity, were present for the past six months.
 - **Predominantly hyperactive impulsive presentation:** If enough symptoms of hyperactivity-impulsivity, but not inattention were present for the past six months.
- Because symptoms can change over time, the presentation may change over time as well.

MANAGEMENT

Tutoring

Management aims at tutoring the child to acceptable behavior and at his training with patience and understanding through behavioral and psychosocial therapy targeted at the child, the parents and the school. The program must involve close coordination among parents, teachers and psychologist.

Pharmacotherapy

The following groups of drugs are available:

- **Stimulant drugs** such as methylphenidate (Ritalin), dextroamphetamine, and magnesium pemoline. Adverse drug reaction (ADRs) of stimulant drugs include anorexia, abdominal discomfort, headache and sleep disturbances.
- **Tricyclic antidepressants** such as imipramine, desipramine.
- **Nonstimulant drug** such as atomoxetine has been recommended as a preferred drug for adolescent ADHD and ADHD with comorbidities and contraindications to stimulants. It is a selective norepinephrine reuptake inhibitor, acting by increasing norepinephrine and dopamine levels, especially in the prefrontal cortex.

- ADRs include change in behavior and suicidal thoughts or actions.
- **Selective alpha-adrenergic agonists** such as clonidine and guanfacine are useful in treating core manifestations of ADHD. ADRs include dryness of mouth, drowsiness, constipation, sleep disturbances, and allergic manifestations. Sudden withdrawal may cause rebound hypertension. In some ADHD cases, stimulant drugs and selective alpha-adrenergic agonists may be combined for better outcome.
- **Phenothiazine's** such as thorazine are also effective in ADHD. Their ADRs include dystonia's.

PROGNOSIS

Prognosis is favorable. Many children do well in adulthood if they are properly employed. The presence of aggression in childhood is a predictive symptom of adult psychopathy in the form of sociopathy, hysteria and alcoholism.

AUTISM SPECTRUM DISORDER

The term, **autism spectrum disorder** (ASD), is the new semantic for the earlier nomenclature, **pervasive developmental disorders**. The disorders included under its umbrella are:

- Autistic disorder
- Childhood disintegrative disorder
- Asperger disorder/syndrome, and
- Pervasive developmental disorder not otherwise specified (PDD-NOS).

Henceforth, a single diagnosis of ASD is required to be made for all the four conditions. Since the molecular basis of Rett syndrome is now known and the causative gene identified, it is not included under this umbrella.

EPIDEMIOLOGY

Prevalence in the USA is approximately 1 in 88; in South Korea it is as high as 1 in 38 children. The prevalence rate of autism in India is 1 in 250 (figure may vary as many cases are not diagnosed). Currently, India appears to be having 10 million people with autism.

Most cases are first born or late born (fourth or more in sibling rank). Boys suffer more often than girls. No epidemiological study has illustrated any association between autistic disorders and socioeconomic status and or vaccine.

ETIOLOGY

First described by Kaner, now ASD is universally regarded as a developmental disability in the same way as CP, learning disability, ADHD are. However, what leads to the developmental disability remains still ambiguous. Different hypotheses are:

- **Genetic predisposition** in view of its occurrence in pairs of identical and fraternal twins. Genetic predisposition is thought to play an important role with contribution from 4-5 genes. Family studies have demonstrated 50-100 times increase in the rate of autism in siblings

of an index child with autistic disorder. Linkage analysis has demonstrated that regions of chromosomes 7, 2, 4, 15 and 19 are likely to contribute to genetic basis of autism. Susceptibility locus is on long arm of chromosome 13 and 17.

- **Neurologic theory** in the form of damage to reticular formation of brainstem about fifth week of intrauterine life (rubella), leading to a window of vulnerability for autism.
- **Organic theory**, based on abnormal brain rhythms in electroencephalogram (EEG), blames a neurologic dysfunction (PKU, infantile spasms, herpes simplex encephalitis) as the cause of autism.

PATHOPHYSIOLOGY

The neuroimaging, neuropathological, EEG and neurochemical findings are:

- Abnormalities in cerebral cortex, especially prefrontal and temporal lobe areas.
- 10–23% of the children with autism show abnormalities on EEG.
- 20–25% of the children show ventricular enlargement on CT scan.
- Increased volume of brain especially in occipital, parietal and temporal lobes. Temporal lobe is considered critical area for the development of autistic disorder. Autistic like syndrome is seen in people with temporal lobe damage.
- Cerebellar hypoplasia with loss of cerebellar granule cells and Purkinje neuronal loss.
- Abnormalities of dopamine, catecholamine and serotonin pathways.

CLINICAL FEATURES

Autism is central to ASD. It is a complex neurodevelopmental and neurobehavioral disability appearing usually in first 3 years of life. Typically:

- The child is highly withdrawn and seemingly living in an isolated world of his own with complete failure to react to other people (impaired social interaction), language deficit with communication problems (impaired communication), extreme aloofness and obsessive desire for sameness in routine and surroundings (impaired imagination).
- In addition, there may be mental retardation, seizures or learning disabilities and other comorbidities. At least 4–32% of these children have grand mal seizures at some point in their life. Approximately, 70% have mental retardation (one-third mild to moderate mental retardation and close to one-half are severely or profoundly retarded).
- The autistic child may have an organic brain disease as in blindness, deafness or mental retardation, or from emotional deprivation. He may, however, be of normal intelligence, some gifted with islands of brilliance. The child's potential is masked and not low or absent.
- Classically, the child takes no interest in environment and is negativistic.

- He fails to develop normal relationship with others, including his mother, and does not react to a situation in an expected manner.
- Lack of eye contact, facial expression and gestures are missing.
- Speech is either poorly developed or not developed at all. About 60% patients develop highly individualized language.
- The child insists on following same routine every day. Some children may be attracted by spinning or rotating objects.
- Response to stimuli may also be unusual. They cannot infer the feelings or mental state of the others around them.
- Some children with autistic disorder exhibit sudden changes in mood with bursts of laughing and crying without obvious reasons. In fact, some behaviors are challenging.
- Some degree of intellectual disability is common. Some areas of ability may be normal, while others may be relatively weak, e.g. cognitive (thinking) and language abilities in particular.

COMORBIDITIES

Box 6.4 list the comorbidities.

DIAGNOSIS

Early identification based by and large on clinical grounds, is of paramount importance. Role of investigation is limited in determining the existence of predisposing or accompanying factors.

In addition to psychological/psychiatric evaluation, speech, language and IQ assessment is warranted.

In some cases, karyotyping, EEG, neuroimaging, etc. may be needed. The important differentials to consider in these patients are childhood onset schizophrenia and mixed receptive-expressive language disorder.

Table 6.1 gives the 5th edition DSM-5 criteria for diagnosis of ASD. The severity of ASD is to be categorized as level 1, 2 or 3.

MANAGEMENT

The management goals include:

Non-pharmacological/General Measures

Multidisciplinary team approach, comprising a pediatrician, psychologist/psychiatrist/social worker, education

Box 6.4 Comorbidities accompanying ASD

- **ADHD:** Full blown or simply hyperactivity and/or inattention.
- **Disruptive behavior:** Self injury, aggression, tantrums.
- **Obsessive-compulsive traits:** Repetitive behavior; sticking to an activity or thought stubbornly.
- **Mood problems:** Depression, swinging of mood (bipolar tendencies).
- **Sleep disturbances:** Impaired initiation, maintenance and early arousal.
- **Seizures:** Generalized, partial, infantile spasm, epileptic aphasia.
- Avoidant-restrictive food intake and narrow food preference, constipation.

Table 6.1: DSM-5 diagnostic criteria for ASD

- Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history.
 - Deficits in social-emotional reciprocity, ranging for example, from abnormal social approaches and failure of normal back and forth conversation; to reduce the sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.
 - Deficits in nonverbal communicative behaviors used for social interaction, ranging for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication.
 - Deficits in developing, maintaining and understanding relationships, ranging for example, from difficulties in adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

Specify current severity: Severity is based on social communication impairments and restricted, repetitive patterns of behavior (Table 6.2).
 - Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive):
 - Stereotyped or repetitive motor movements, use of objects, or speech (e.g. simple motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
 - Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g. extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
 - Highly restricted, fixated interests that are abnormal in intensity or focus (e.g. strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest).
 - Hyper or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g. apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
 - Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).
 - Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
 - These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.
- Note:** Individuals with a well-established DSM-4 diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.
- Specify if:
- With or without accompanying intellectual impairment
 - With or without accompanying language impairment
 - Associated with a known medical or genetic condition or environmental factor
 - Associated with another neurodevelopmental, mental, or behavioral disorder.

specialist and parents should revolve around the following strategies:

- Management of abnormal behavior (behavior modification).
- Help for the family.

Pharmacotherapy

There is no medication to treat autism as such. However, appropriate medication is available for specific symptoms and comorbidities like aggression, temper tantrum, depression, anxiety, ADHD, self-injurious behavior, sleep disturbances, obsessive-compulsive disorder (OCD) traits and seizures.

- **Neuroleptics** (risperidone, olanzapine, ziprasidone) may be selectively employed to relieve such comorbidities as disruptive behavior in the form of self-injury, aggression and tantrums.
- **Central nervous system (CNS) stimulant** such as methylphenidate for disruptive behavior, neuroepileptic, risperidone for bipolar mood disorder, serotonin-specific reuptake inhibitors (SSRIs), fluoxetine, fluvoxamine.
- **Vaccination:** Norms for routine immunization remain same as in other children. Measles, mumps and rubella (MMR) vaccine can be safely given despite the controversy some years back.

Prognosis

Prognosis is guarded. With early diagnosis, improved care, and intensive behavioral therapy, the proportion of subjects who become self-sufficient and conduct fairly well in the society is on the rise. Presence of functional speech and good IQ favors better prognosis. Nevertheless, many autistic children end up in institutions sooner or later.

ASD AS A COMMUNITY CHALLENGE

Worldwide, including India, a movement has erupted for promoting the cause of autistic children and advocacy for them.

SOCIAL COMMUNICATIVE DISORDER

This newly designated disorder by DSM-5 refers to children who present with only social-communication problems and do not display the repetitive and stereotyped behaviors of ASD.

In other words and to be explicit, social communicative disorder (SCD) includes difficulties in verbal and non-verbal communication and is distinct from ASD. The child may have only social communication difficulties such as getting very close to others when they speak, not modulating their

102 voice and not taking turns in conversation. The diagnosis of SCD is the right one for them, not the ASD.

Let it be clear that a diagnosis of SCD should be considered for children who have sheer social-communication problems. They fail to meet the DSM-5 criteria for ASD.

CEREBRAL PALSY

Cerebral palsy (CP) is a form of chronic motor disability which is non-progressive, non-fatal and yet non-curable and results from damage to the growing brain before birth, during birth, or after birth.

Convincing evidence is now available to show that birth asphyxia, earlier believed to be a leading cause of CP, is, in fact an uncommon etiologic factor in this entity.

Current thinking is that roots of pathogenesis of CP may well be in the developmental biology. For details, See Chapter 23 (Intrauterine Infections).

BEHAVIORAL DISORDERS

GENERAL CONSIDERATIONS

Behavioral problems include disorders that represent significant deviation from the normal behavior. These disorders are relatively stable, internalized and difficult to treat than the adjustment reactions, but less than neurosis and psychosis. The hyperkinetic reactions, runaway reactions and group delinquency are examples of behavioral disorders.

CATEGORIZATION

Boxes 6.5 and 6.6 categorize various behavioral disorders.

GENESIS

The root cause of the problem usually is traceable at home and/or at the school environment.

When the parents report a solitary symptom in the absence of any other major illness in the child, it is classified as **special symptom**. Common examples of this category are nail biting, thumb sucking, somnambulism and enuresis.

Since a situational aberration (usually in the family or at school) is a common denominator of the background

Box 6.6

Categorization of behavioral problems in relation to age group

- **Infancy:** Feeding problem, colic, stranger anxiety, breath-holding spells, temper tantrum.
- **Preschool age:** Head banging, body rocking, thumb sucking, nail biting, masturbation, lack of clarity of speech.
- **Midchildhood:** Stuttering, pica, sleep problems, enuresis, encopresis, tics.
- **Adolescence:** Juvenile delinquency.

of adjustment reactions, behavioral problems and special symptoms; it is customary to label all these as **behavioral disorders**. Factors contributing to behavioral problems are given in Table 6.2.

The etiology of behavioral disorders is multifactorial, including maladjustment at home and/or school, and factors operating before pregnancy, during pregnancy, during delivery and in neonatal period. A faulty emotional environment (constituted by parental attitudes, siblings, neighborhood, school and mass media, including television, radio and periodicals) is, however, most important.

Of the environmental factors, faulty parental attitudes (rejection, overprotection, dominance, unrealistic expectations, over criticism, discrimination, unfavorable comparison, over or under discipline, dominance by the parents, marital disharmony, etc.) are the single most vital cause of behavioral difficulties.

Overprotection means more than excessive protection of the child against danger with the result that he is not allowed to take care of him and grow up like his peers who are given balanced protection. It may happen in the only child, the only son in particular, a child born after many years of waiting, the first born, especially in a joint family, a very good-looking child, a mentally retarded or physically handicapped child, in case of loss of a spouse or failure on the part of the spouse to play his or her role well, or a child who is supposed to have brought fortune to the parents.

Rejection, on the contrary usually is accompanied by failure to attend to the normal needs of the child, unfavorable comparisons and admission to an institution when the circumstances do not really demand it, unnecessary scolding, excessive punishment, or failure to please the child consistently with a reward as and when appropriate. There is invariably accompanied favoritism to the other-child.

Box 6.5 Categorization of common behavioral problems

- **Habit problem:** Thumb sucking, nail biting, tics, enuresis, encopresis, trichotillomania, breath-holding, aerophagia.
- **Problems of eating:** Pica, food fads, food refusal/overeating, vomiting, aerophagia, anorexia.
- **Sleep problems:** Night terrors, nightmares, somnambulism, insomnia, sleep-talking, hypersomnia, narcolepsy, cataplexy.
- **Speech problems:** Stammering, stuttering, mutism, phonation and articulation disorders.
- **Scholastic problems:** Reading, writing or mathematical disability, repeated failures, absenteeism, truancy, school phobia, aggressiveness.
- **Sexual problems:** Masturbation, homosexuality, incest, precocious sexuality, hypersexuality.
- **Personality problems:** Shyness, timidity, fears, anger, jealousy.
- **Antisocial problems:** Juvenile delinquency in the form of stealing, lying, destructiveness, cruelty, gang activities, etc.

Table 6.2: Factors associated with behavioral problems

Child

- Health
- Development
- Coping mechanism

Parents

- Misinterpreted behavior
- Mismatched expectations
- Parenting style
- Coping mechanism

Environment

- Stress
- Support

Rejection may happen to an unwanted child, an illegitimate child, a stepchild, a mentally or physically handicapped child, a child who is supposed to have brought bad luck to the family, or a child who is chronically mischievous and a constant source of troubles for the family.

Not infrequently, parental attitudes may well be a cocktail of overprotection and rejection at different times, depending on such diverse factors as parents' mood, financial position, job satisfaction, and interparental relationship. Lack of consistency on the part of the parents confuse the child, leading to conflict, anxiety and insecurity.

PRINCIPLES OF COUNSELING

- According to the dictionary, *counseling means providing of advice and guidance to a patient by a health professional.*
- It is a useful intervention for many behavioral disorders, aiming to affect a change in behavior.
- To be of real benefit, the change should be learned and not imposed.
- Paradoxically, however, the intended change in behavior is often imposed on children and/or parents. Hence, a high chance of failure.
- Secondly, while counseling for a change in behavior, any attempt at invoking a guilt feeling should be avoided.
- Once the intended behavioral change is learned, it needs to be reinforced to make it permanent. Spending 15-30 minutes daily for a positive child-parent interaction is useful. Generally speaking, mothers are expected to perform this role. However, it is desirable that the father too take interest and responsibility in this pursuit. After all, often the unresolved conflicts in the child relate to the relative role played by both parents.
- Counseling should also aim at diffusing the guilt feeling in parents.
- Among others, the following two approaches are helpful in this behalf.
 1. Bringing to their knowledge the cases of many other parents with similar problems and providing guidelines for coping with them.
 2. Increasing the support circle, e.g. letting several mothers with enuretic children discuss the problems among themselves.

The field of child psychiatry primarily deals with identification and handling of the emotional, behavioral and developmental disorders of childhood. Its knowledge in case of a pediatrician is of particular importance, at least for two reasons.

- **First**, his first contact with the child and his parents and the subsequent contacts uniquely contribute to evaluating the development of the child and advising the parents about his upbringing.
- **Secondly**, it is vital for him to identify psychosocial or psychotic problems not only for managing these, but also for seeking psychiatric consultations as and when indicated. Symptoms in childhood psychiatric disorders are subtle and are likely to be passed off

as normal variants. Even in frank cases, parents are reluctant to consult a psychiatrist due to social taboos.

No doubt, the field of child psychiatry helps him to understand the child through and through as a living, acting, feeling, and choosing to be. He is unlikely to fulfill this function completely and earnestly without the knowledge of fundamentals of child psychiatry.

EATING DISORDERS

RUMINATION DISORDER (Rumination Syndrome)

It is a chronic condition characterized by repeated effortless regurgitation and chewing of feed or meals over a period of at least one month.

- **Etiology:** It lies in disturbed relationship with parents/caregivers and non-stimulating environments.
- **Clinical features:** Two types are recognized:
 1. **Physiologic:** In normal infants, occurring usually in 3-6 month age group.
 2. **Pathologic:** In infants with mental retardation (usually severe) and ASD.

The hallmark of rumination is malnutrition, weight loss and growth delay.

- **Differential diagnosis:** It includes gastroesophageal reflux (GER), pyloric stenosis, Sandifer syndrome (tonic posturing, GER), raised intracranial pressure, inborn errors of metabolism, etc.
- **Treatment:** Reinforcing correct eating behavior.

PICA (Geophagia)

The term, pica (Latin: magpie), refers to eating of substances other than food (non-edible/non-nutritive items), e.g. clay, earth, dust, sand, flakes of paint, plaster from wall, soap, paper, fabrics, ice (pagophagia), etc. It is frequent in the first four years of life, but may be seen in grown-ups as well. Pica as a manifestation of inclination for mouthing and tasting in the absence of any associated problem may be taken as normal until two years of age. Thereafter, it may well be considered a deviant behavior requiring attention. Incidence is high in intellectually-disabled children.

- **Etiology:** An association of pica with mental retardation is a category per se. Here we are largely concerned with pica in otherwise normal children. In the latter situation, pica usually occurs in children from the lower strata of society with suggestions of parental neglect and even abuse, poor supervision or proper attention. Associated malnutrition with worm infestation and vitamin and mineral deficiencies is common. Whether these are the cause or effect of pica remains unclear.
- **Clinical features:** These infants and children are often anemic primarily because of iron deficiency anemia (IDA) and have mineral and vitamin deficiencies. Intestinal parasitic infestations are generally associated. Some develop pseudotumor cerebri. Besides, there is a risk of chronic lead poisoning which can be dangerous.

104 Also, behavioral problems are common. Some children may pull out their head hair (trichotillomania) and swallow them. Lots of hair may collect in the stomach, which becomes palpable as a big lump in the upper abdomen (trichobezoar), particularly after meals.

The perverted appetite in such children is generally a manifestation of psychologic cause which should be searched.

- **Treatment:** In view of the common association between pica and worm infestation plus vitamin and mineral deficiencies (IDA in particular), it is necessary that treatment of these factors receives attention at the earliest.

Psychotherapy (especially behavior modification) is of value in cases where pica is associated with psychosomatic problems.

ANOREXIA NERVOSA

An eating disorder characterized by:

- An abnormally low body weight (<85% of expected for age),
- Intense fear of gaining weight,
- A distorted perception of body weight and body image, and
- Amenorrhea in postmenarcheal girls.

Teenagers with anorexia nervosa place a high value on controlling their weight and shape, using extreme efforts (restricting diet and indulgence in too much exercise) that tend to significantly interfere with activities in their lives.

- **Clinical features:** Two clinical types are
 1. **Restrictive:** The patient not only severely restricts the amount of food intake, but also controls calorie intake by vomiting after eating or by misusing laxatives, diet aids, diuretics or enemas. They may also try to lose weight by exercising excessively.
 2. **Non-restrictive:** The patient with anorexia binges and purge as in bulimia nervosa. However, people with anorexia generally struggle with an abnormally low body weight, while individuals with bulimia typically are normal to above normal weight. No matter how weight loss is achieved, the person with anorexia has an intense fear of gaining weight.

Accompanying manifestations include anxiety, depression, OCD, suicidal tendencies, and nutritional deficiencies. Frequently induced vomiting and abuse of diuretics and purgatives may cause metabolic acidosis.

- **Complications:** Cachexia, metabolic acidosis.
- **Treatment:** It comprises psychotherapy, often along with antidepressant and antipsychotic agents. For severely malnourished subjects, nutritional rehabilitation, preferably in a health facility, is essential.

BINGE EATING

Binge eating disorder is a serious eating disorder in which the patient frequently consumes unusually large amounts of food. In fact, overeating crosses the limits. In due course, it becomes a regular occurrence, usually carried out secretly.

BULIMIA NERVOSA

An eating disorder characterized by binge eating and purging. The subject consumes a large amount of food in a short amount of time followed by an attempt to rid himself of the food consumed (purging). Purging is attained by self-induced vomiting, taking a laxative or diuretic, fasting and/or excessive exercise.

- **Etiology:** There is an extensive concern for body weight. Many individuals with bulimia nervosa also have an additional psychiatric disorder.
- **Comorbidities:** Common comorbidities are mood disorders, anxiety, depression, impulse behavior, and substance abuse disorders. Family histories of alcohol and substance abuse, mood and eating disorders may be present.
- **Treatment:** It revolves around psychotherapy along with antidepressant and antipsychotic agents.

FOOD FUSSINESS

It is defined as **avoidance of food stuff for one or the other flimsy reason by children**. It is quite a common problem, causing anxiety to parents.

- **Etiology:** Factors contributing it include overindulgence by parents who may well be themselves fussy eaters, at least in the past.
- **Management:** It revolves around such behavioral strategies as:
 - A pleasant, conducive atmosphere at main meal time which should be regular
 - Avoiding force feeding
 - A pleasant presentation of foods
 - Offering small to moderate serving at a time
 - Avoiding eating energy foods in between main meals
 - Parents and other family members setting example by good eating behavior, avoiding critical comments about the food being served.

BAD TOILET TRAINING AND ITS PROBLEMS

By 2–2½ years of age, the child tends to point to fullness of bowel and bladder. This is the time to begin toilet training in the form of simple instructions given in a holistic manner. Patience and positive reinforcement are key to its success. In no case, parents should use force or pressurize him. Use of a comfortable potty or a toddler-size seat fitting on regular toilet seat is advisable in order to make the child confident, comfortable and secure. Most toddlers take about 3 months for training though they are likely to need some help for washing/cleansing body part up to 5 years of age or so.

The child's toilet training experience should be positive. If it becomes a struggle or a battle of wills between him and parents, it is best to ease up or discontinue for a short span. Although parents may be ready for toilet training, the child may not be.

Failure to conduct proper toilet training at appropriate age (usually after attaining 2–2½ years of age) may result in

difficulties such as refusal to pass motion and development of constipation.

ELIMINATION DISORDERS

ENURESIS

(Bedwetting)

The term, enuresis, denotes normal urinary bladder emptying at a wrong place and time at least twice a month at or after the age of 5 years.

Nocturnal enuresis refers to bedwetting. It is a fairly common pediatric problem, occurring in about one-fourth of children, and is a potential cause of embarrassment to the child as well as the parents. A proportion of children suffering from this disorder may wet their garments during waking hours as well (diurnal enuresis). Boys suffer more often than girls. Remarkable familial pattern is observed.

Types

Four types are recognized based on day-time symptoms:

1. **Type I:** Monosymptomatic nocturnal enuresis
2. **Type II:** Diurnal enuresis without day-time frequency
3. **Type III:** Nocturnal enuresis with day-time frequency
4. **Type IV:** Nocturnal diuresis with day-time frequency and voiding dysfunction.

Clinical Features

Two clinical types are recognized—(1) primary (persistent) and (2) secondary.

- In the **primary (persistent) enuresis**, the child has never been dry at night. It is usually the result of erratic bladder training either by parents who are overanxious for prompt control, or those who are not reasonably close to the child's needs, or chronic psychological stress not related to bladder training.
- **Secondary (regressive) enuresis** is characterized by initial control of bladder that later gets disrupted by stressful environmental events like marital conflict, death, arrival of a sibling, or shifting to a new house. It is usually intermittent and transitory.

Etiology

The causes of enuresis are:

- Psychologic enuresis may be a manifestation of family conflict and maladjustment, e.g. too strict parents, rejection, sibling rivalry, etc. An erratic handling of the problem by the parents causes further anxiety to the child. His condition, therefore, gets more aggravated.
- Too late, too early or improper training by the parents regarding the bladder control is also an important factor in the causation of bedwetting.
- Physical factors like threadworm infestation, genitourinary infections, anatomic defects, etc. may be responsible for enuresis in some cases.

In both types (primary and secondary), an organic pathology is present in less than 5% cases. Dysuria, frequency, straining, dribbling, gait disturbances and poor bowel control suggest an underlying organic cause.

Box 6.7 DSM-5 criteria for enuresis

- Repeated voiding of urine into bed or clothes (whether involuntary or intentional).
 - Behavior must be clinically significant as manifested by either a frequency of twice a week for at least 3 consecutive months or the presence of clinically significant distress or impairment in social, academic (occupational), or other important areas of functioning.
 - Chronological age is at least 5 years of age (or equivalent developmental level).
 - The behavior is not due exclusively to the direct physiological effect of a substance (such as a diuretic, antipsychotic or selective serotonin reuptake inhibitors (SSRI)) or to incontinence uncured as a result of polyuria or during loss of consciousness.
 - These symptoms must not be due to a general medical condition.
- Specific types:** Nocturnal (night-time) only, diurnal (day-time) only, nocturnal and diurnal.

Note: All of the DSM-5 criteria must be met in order to diagnose enuresis in an individual.

Diagnosis

This should include a detailed interview with the parents as well as the child to find the etiologic or, at least, associated emotional factors, together with a complete physical examination. Intestinal parasitosis, especially threadworm, genitourinary infection and anatomic defects should be excluded.

Urine analysis and urine culture should be performed at the initial visit to exclude urinary tract infection (UTI). An X-ray of lumbosacral spine, ultrasonography, voiding cystourethrogram and urodynamic studies are often required. Box 6.7 lists the DSM-5 criteria for enuresis.

Treatment

A prompt treatment is essential or the child may continue to have enuresis plus added emotional problems in adolescence. Treatment is, as a rule, not required before 6 years of age.

If the underlying disease is detected it should be treated. In others, treatment consists of:

- **Psychotherapy and training (behavior modification)** in the form of:
 - Reassurance to the parents and the child. Parents should be told to encourage the child in having dry nights. In fact, they should offer special pat and even reward on occasions when the child does not wet the bed.
 - Restriction of too much of water and drinks at bed time and insisting on his voiding before retiring.
 - Waking him up once or twice to void during night.
 - Rewarding the child for the dry nights (which should be charted on a calendar) assists in enlisting the cooperation of the child.
 - Discouragement of punishment or humiliation of the child by the parents.
 - Ridicule by siblings and friends should not be allowed. Parents need to spend at least half an hour of quality time with the child.
- **Bladder-strengthening exercises:** This includes emptying the bladder before sleeping, drinking large quantity of water during day-time and holding urine as long

as possible and practice repeatedly starting and stopping the stream in the flush.

- **Using an electric alarm (buzzer) device:** The buzzer is designed in such a way that the child wakes up as soon as he is about to wet the bed. The device is based on the condition reflex response. It consists of a sensor fixed to child's underwear and an alarm placed at bedside.
- **Drugs**
 - Imipramine hydrochloride, 0.9–1.5 mg/kg/day orally (O) at bedtime for 3–6 months, gives good results. It acts by altering the arousal-sleep mechanism. The success rate considerably improves if it is supplemented with a small dose of diazepam.
 - Anticholinergic agent, oxybutynin, 10–20 mg/day O, for 3–6 months, is useful for day-time enuresis with urgency and urges incontinence. It acts by reducing the uninhibited bladder contractions.
 - Desmopressin (DDAVP)*, a synthetic antidiuretic agent, is a relatively expensive modality for enuresis. The basis for use of this drug is that immediate triggering factor for enuresis is the over distended bladder, resulting from reduced secretion of the ADH rather than the abnormal bladder capacity or function. It is given in full dose (10–40 meg/day) as spray until child is dry for 28 successive nights. Thereafter, dose is tapered over three weeks' period.

At times, a combination of modalities (says behavior modification, electric alarm device plus drug therapy) work best. The pediatrician must also develop a positive relationship with the child to allay feeling of guilt, resentment or shame. He should motivate the child for independent control.

Finally, there are reports of effectiveness of the complementary and alternative medicine (CAM) in the form of Chinese acupuncture and herbs.

ENCOPRESIS

Encopresis, indicating a more serious emotional disturbance than enuresis, is characterized by passage of feces into inappropriate places at any age (usually after 5 years) when bowel control is expected to be accomplished.

- In **primary encopresis**, chronic soiling persists from infancy onward.
- In **secondary (regressive) encopresis**, soiling occurs after attaining bowel control at appropriate age. Accompanying symptoms include chronic constipation, fecal impaction, overflow incontinence, and poor school attendance and performance.

The cause is subconscious anger and defiance in the child. Children with autism are more likely to have encopresis.

Treatment is similar to that of enuresis as far as supportive measures are concerned. Primary encopresis is more difficult to treat than the secondary form. Hirschsprung's disease is considered in the differential diagnosis of encopresis.

* DDAVP: Deamino-Delta-D-Arginine Vasopressin

BREATH-HOLDING SPELLS (BHS)

(Infantile Syncope)

This common situational disorder is characterized by the development of cyanosis/apnea or pallor after a bout of crying from provocative events like anger, pain or frustration. It accounts for 4–13% of psychosomatic disorders in pediatric age group. The condition occurs to some degree in upto 27% of otherwise normal children. In a vast majority, onset is before 18 months of age.

Two types are recognized—(1) cyanotic and (2) pallid. Cyanotic type is thrice as frequent as the pallid type. In 20% of cases, both types may coexist.

ETIOLOGY

The time-honored belief is that breath-holding spells (BHS) result from frustration on the part of the child. A disciplinary conflict between parents and the child is the basic underlying cause. The child uses the attack or its threat to assert him and to express his anger or protest.

According to a recent explanation, genetically determined dysregulation of autonomic nervous system reflexes is responsible for BHS. Different autonomic dysregulatory mechanisms are responsible for the two types of BHS.

1. The **pallid type** is supposed to be secondary to cardiac asystole, similar to a vasovagal attack. It can be induced by ocular compression.
2. The **cyanotic type** results from a rise in intrathoracic pressure when breath is held in expiration (as, for example during crying), leading to decrease in cerebral circulation. The mechanism involves interplay among hyperventilation, Valsalva maneuver, expiratory apnea and intrinsic pulmonary mechanisms.

Cerebral anoxia from an autonomic dysfunction is responsible for the loss of consciousness. Though the beginning of the attack is voluntary, subsequent loss of consciousness is involuntary. Role of IDA too is speculative. The association between BHSs and IDA is well known. Anemia seemingly adversely affects the compensatory functions of autonomic nervous system and contributes to cerebral anoxia in severe BHSs. Treatment of IDA in many of them may promptly and fully stop the spells.

CLINICAL FEATURES

- **Classical attack (cyanotic type):** The child cries, hyperventilates and holds his breath (usually in expiration) followed by cyanosis in a few seconds. There may occur momentary loss of consciousness and convulsive twitching. Finally he becomes limp.
- **Pallid type:** The child develops characteristic pallor rather than cyanosis.

The onset in both the types is between 6 and 18 months of age. The frequency is usually one to three attacks a day.

DIAGNOSIS

Clinical picture comprising of classical sequence of **crying-cyanosis or pallor-brief loss of sensorium** is usually so characteristic that little difficulty should be encountered in recognizing the condition.

DIFFERENTIAL DIAGNOSIS

- **Epileptic attack:** When spells are accompanied by tonic and clonic seizures, differentiation from epilepsy becomes essential. In the former, an obvious precipitating factor can invariably be elicited. Secondly, cyanosis in spells precedes convulsions whereas in epilepsy it follows these. Thirdly, EEG in spells is invariably normal.
- **Hypercyanotic spells:** Breath-holding spells should also be differentiated from cyanotic attacks seen in congenital heart disease.
- **Cardiac arrhythmia/prolonged QT syndrome:** Electrocardiography (ECG) is helpful in excluding it in the case of doubts.
- Brainstem malformations.

TREATMENT

- It is directed at determination of the causative and precipitating factors and treating these by psychotherapy.
- Attention must be directed to correction of coexisting IDA.
- Drug therapy is of insignificant value. Very frequently occurring pallid BHSs may respond to atropine sulfate, 0.01 mg (O), thrice daily. Response to piracetam, an expensive agent, too is quite gratifying.

PROGNOSIS

As the child grows, frequency of spells decreases. Finally, almost all such children are symptom free by the age of 5 or 6 years.

Incidence of temper tantrum and other behavioral disorders in these children is high. There is no evidence that epilepsy occurs in greater proportion in them than in the normal population.

HABIT DISORDERS

Habit disorders are a very common problem in children. Over 20% children are known to exhibit these sooner or later.

THUMB SUCKING

This is normal in first three years of life, showing peak incidence in the second half of the second year. Thumb sucking beyond the age of 3–4 years may adversely affect the teeth, causing malocclusion, in a proportion of children. Besides, it is not socially acceptable.

Parents need to distract the child's attention and motivate him against the habit. Scolding or punishing the child is likely to worsen the situation. Application of noxious agents over the child's thumb, a common practice, is not recommended.

NAIL BITING

A stress-relieving habit, nail biting is a phenomenon demonstrated by children beyond four years of age. It may continue upto adolescence and even in later life.

The cause is a kind of insecurity, a conflict or hostility. The child seemingly draws a sense of pleasure from such self-stimulations.

Risks involved are:

- Soreness of fingers
- Deformed nails
- Infection of the nailbed
- Transmission of pathogens by feco-oral route.

Chronic nail biting should be discouraged. Parents need to ensure that child's nails are regularly cut. He may be offered a reward for checking the habit and allowing growth of the nails. At the same time, attempt should be made to find out the source of stress such as an overstrict teacher or bullying by a peer. Wearing gloves or adhesive bandages may be helpful in some cases.

Treatment consists in reassurance to the parents and guidance that they need not be fussy over these benign problems.

TEETH GRINDING (BRUXISM)

Bruxism among children, especially during sleep, is a common observation. In case of infants, one need not bother about it. In older children, it may be a manifestation of disturbing dreams, pent-up tension and aggression. Apart from this, bruxism may occur in mental retardation and in unconscious patients, more so those suffering from meningitis or encephalitis. There is no evidence that bruxism has any relationship with worm infestation.

Treatment consists in improving the environmental situation responsible for the tension and conflict. Attempts should be made to make bedtime more enjoyable and relaxed. Watching of thrillers and horror shows at bedtime should be avoided.

STUTTERING

Preschoolers, generally 3–5 years of age, may start stammering. The cause in a large majority of the cases is the neurotic attitude of the mother. It is an indication of a conflict in child's personality.

No treatment is generally needed. If stuttering persists, breath-control exercises and miniaturized metronome that is of value in pacing the rhythm of speech need to be resorted to under care of a speech therapist.

TICS (HABIT SPASM)

The term refers to fast repetitive movements which are frequently stereotyped and are alterable at will. Tics occur most often in school going children and usually represent an emotional disturbance or maladjustment. Generally, they may be an outlet for the suppressed anger and tension following control of aggression by the parents or the teacher.

108 Tics in the form of involuntary purposeless movements such as eye blinking, throat-clearing, facial twitching, etc. are seen in school-aged children. A socially unacceptable form of ticks is obscene gestures and vocalization.

A kind of tics in which extensive and varied bodily movements are accompanied by vocalization (barking or shouting obscene words) has been termed **Gilles de la Tourette syndrome**.

Distraction is the best way out in most varieties of tics. Severe variety of tics requires psychiatric evaluation. In Tourette syndrome, 1–5 mg haloperidol, given orally daily, as such or together with an anti-parkinsonian drug, is indicated.

DISRUPTIVE BEHAVIORAL DISORDERS

Disruptive behavioral disorders (DBD) is defined as a behavior that brings a child into conflict with his environment. Such disorders are:

- Temper tantrums
- Oppositional defiant behavior
- Juvenile delinquency.

TEMPER TANTRUMS

The term, **temper tantrum**, denotes throwing different forms of tantrums as a protest to certain challenges (physical or emotional) and to draw attention to himself. The odd behavior is a manifestation of his frustration and negativism which is not able to express because of poor verbal skills and command.

Tantrums may be in the form of loud crying, yelling, head-banging, kicking, hitting, pushing, throwing away objects, etc.

Classically, these start at 1.6–2 years of age and subside by 3–6 years. Management comprises:

- Avoiding situations in which disruptive behavior may occur.
- In the midst of tantrum, parents must demonstrate a calm, but firm behavior.
- Protecting the child from injury.
- Distraction from immediate cause and changing environment.
- Allowing child's stay in a safe, quiet place for some minutes (timer-out).

OPPOSITIONAL DEFIANT DISORDER

It is defined as a behavior which is characterized by persistent and repetitive opposition, stubbornness, disobedience, defiance and disruptiveness towards parents and/or other authorities spread over a minimal of 6 months.

- **Etiology:** It can be traced to a serious conflict between parents and their reactions, environmental factors and child's personality traits. Family background often suggests presence of AHD, depression or an antisocial personality disorder.
- **Treatment:** It revolves around resolution of parental conflicts, environmental factors and child's anger management. Central nervous system (CNS) stimulant may be effective.

CONDUCT DISORDER

It is defined as a repetitive and persistent aggressive and destructive behavior that causes disruptions at home, neighborhood or school over a minimal of 6 months period. Management is directed at:

- **Parents:** Positive reinforcement to improve behavior, extinction and time out to decrease problem behavior.
- **Children:** Anger-coping, peer-coping and problem-solving skills.

JUVENILE DELINQUENCY

The term, **juvenile delinquency**, denotes indulgence in an offense by a child, precisely less than 18 years of age. In case of serious crimes, age limit has now been reduced to 16 years in India. Besides, such crimes as sexual assault, murder, burglary, theft and inflicting injuries on others, the term includes relatively minor deviations of youthful behavior, e.g. say desertion of family and mixing with antisocial gangs and ungovernable habitual disobedience.

In keeping with the increasing youth unrest over the recent decades, incidence of juvenile delinquency in India is on the increase. Boys are involved 4 to 5 times more than the girls.

Etiology

Disturbed family conditions, e.g. disharmony between the parents with constant quarrels, divorce, death, poverty, alcoholism, lack of discipline or far too much of it, and too many children are the most prominent amongst the causes of juvenile delinquency. Next comes, the unsatisfactory conditions at school or college, say lack of adequate recreational facilities, lack of channelization of adolescents' energies, unhealthy teacher-taught relationship, etc. Finally, there is an evidence that certain biologic causes like hereditary and chromosomal defects, physical defects and feeble mindedness may be at the bottom of personality disturbance, leading to delinquency.

Prevention

Prevention should aim at improvement in family conditions so that the child is brought up in an atmosphere of understanding, love and balanced discipline, improvement in the school/college atmosphere with availability of adequate sports and recreational facilities and loving teacher-taught relationship and provision of child-cum-parents counselling facilities.

Management

There is an evidence that positive family and parental interventions cut down criminal behavior by juvenile delinquents. Foster family care may also be helpful.

No one is born with delinquency. The malady is the result of interaction of many factors related to home environment, school and society. Just because a delinquent fails in his duty to the society, we are not absolved of our duty to him.

SLEEP WALKING

(Somnambulism)

Loafing around aimlessly during sleep is, by no means, rare in childhood. According to one estimate, somnambulism occurs in about 5–8% of children. Such children are aware of the environment during the episode, but are indifferent to it. They resent all attempts to arouse them during the act.

Once awake, they remember almost nothing about the episode. There are several familial instances of somnambulism. Preventive measures include locking the doors and windows, removing dangerous objects and correction of superstitions. Small doses of diazepam are of value in advanced cases.

SCHOOL PHOBIA

(School Refusal, School Withdrawal)

School phobia refers to absolute refusal by the child to go to school.

The major underlying factor is anxiety about separation from the parents, most often the mother. The parents are responsible for giving the child an impression that school is a place to be dreaded and that they won't indeed mind his staying at home. There usually is a far-too-close tie between the child and the parents. The mother is overindulgent, overprotective and domineering type and the father is ineffective and disinterested.

Such school factors as bullying or teasing, unreasonable punishment or dislike by the teacher may also contribute to the problem.

Treatment consists in weaning the child and the parents from each other with the help of a child psychiatrist and family physician. The cooperation of the school teacher(s) should be obtained as and when warranted.

DRUG ABUSE

(Substance Abuse)

Drug habit is no longer a rarity among the adolescents of developing countries. All India surveys indicate as high an incidence as 3% of **addiction** and 15% of **casual indulgence** among senior school going students. The prevalence is particularly high in boarding public schools.

The drugs generally abused are alcohol, tobacco, sleeping pills, tranquillizers, central stimulants, mood-elevators, cannabis (*bhang, charas, ganja*) and opiates. lysergic acid diethylamide (LSD), cocaine and heroin are used by a much smaller proportion of abusers. The majority uses more than one drug.

Most of the addicts show significant evidence of conflict, confusion, mental tension and remarkable deterioration in academic performance. Shoplifting, stealing and, at times, even trafficking is resorted to by the diehard addicts to make enough money for procuring their supply of drugs.

WHY DRUGS?

- The causes include frustration at home, poor performance at school, bad company and emotional stress.

- "Keeness to burn midnight oil" at the time of examination and to gear up stamina for better performance in sports and athletics are said to be the stimulus to take drugs with some.
- Others indulge in the word of drugs "just for kicks", just for the heck of it, simply to see what will happen or as an adventure.
- Yet another group consumes drugs to "hit back" at the parents, teachers or society-in protest indeed. To check the malady, the recommended measures include:
 - Provision of adequate facilities for recreation and entertainment, especially in the hostels.
 - Proper channelization of energies of the adolescents into constructive activities.
 - Inculcation of the dangers of drug abuse among students, their teachers and family members.
 - Provision of periodical psychiatric guidance facilities in schools.
 - Strict implementation of drug control measures. Also See Chapter 4 (Growth Disorders).

PERIODIC SYNDROME

The disorder refers to periodic occurrence of certain symptoms such as colicky abdominal pain (periumbilical) nausea and vomiting, headache (often of migraines variety), diarrhea or constipation, marked pallor or flushing, fever and prostration. These manifestations may be present in various combinations.

A characteristic feature of the syndrome is that recurrences occur at a different periodicity of weeks or months. In between the attacks, the child is all right.

The patients are usually emotional, highly strung, obsessional and perfectionists. Their parents' expectations are far too lofty. A quarrel in the family or school examination often precipitates the attack. There is, as a rule, no evidence of infection. In a small proportion, there may be evidence of epilepsy.

Treatment consists in providing assistance with emotional stress in the family or school. Regular psychotherapy may be warranted in hard cases.

HYSTERIA

(Hysterical Conversion Reaction)

In hysteria, now recognized as a dissociative (conversion) disorder, the child (usually a pre-adolescent or an adolescent) with a psychopathic personality presents with manifestations simulating an organic disease, say recurrent abdominal pain, sensation of compression of the throat (globus hystericus), blindness, gait disturbances, paralysis, sensory loss, urinary retention, seizures or dyspnea.

A good history-taking and clinical work-up usually leads to the correct diagnosis without resorting to painstaking investigations. The patient has a tendency to be indifferent to the queries and relates manifestation in a detached manner.

110 Common Presentations

- **Hysterical seizures**, a common presentation are remarkable by absence of tongue-biting, apnea and incontinence. The patient tends to forcibly hold the eyes closed and seizure activity is bizarre. Quite often, seizures are marked by rhythmic thrusting and writing of trunk. Nocturnal seizures, stereotyped aura, cyanotic skin changes and postictal confusion are infrequent in pseudoseizures of hysteria. Moreover, serum prolactin level remains normal after the pseudoseizures. EEG too shows no spike and wave forms or postictal slowing.
- **Hysterical blindness** is characterized by tunnel vision and absence of pupillary abnormality and fundoscopic abnormality.
- **Hysterical ataxia** is characterized by an inability to stand or walk without any deficit on neurologic examination when tested in lying-down position. The gait is bizarre and there is an extreme lurching on the sides. In cerebellar ataxia, on the other hand, the patient walks on a wide base and has difficulty in maintaining balance.
- **Hysterical paralysis** is characterized by the presence of normal muscle tone, tendon reflexes and plantars, and positive Hoover test. The last named consists in keeping hand under the allegedly paralyzed leg and asking the patient to raise the normal leg against resistance. As the patient forcefully lifts the leg, the examiner's hand can feel downward pressure of the affected leg against the examiner's hand. This occurs only in hysteria.
- **Hyperventilation syndrome** is a state characterized by dyspnea, tightness or stabbing pain in chest, headache, abdominal pain, muscle pains, paresthesia, palpitations, and dryness of mouth, vertigo, choking, weakness, blurred vision, confusion and syncope. The syndrome occurs in episodes. The causes include acute anxiety state, uremia, salicylate poisoning, hypernatremic dehydration, diabetic ketoacidosis, and Reye syndrome. Treatment is primarily of the cause.

Management

Treatment of hysteria is primarily early detection and symptom removal. The symptom removal (normalization) can be attained by insisting on adherence to routine and contracting differential reinforcing and removal of secondary reinforces. The child should never be accused of feigning the symptoms. Appropriate antidepressants and anxiolytics may be warranted.

PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME

Pediatric acute-onset neuropsychiatric syndrome (PANS) refer to an abrupt, dramatic onset of OCD or severely restricted food intake coincident with the presence of two or more neuropsychiatric symptoms. The diagnostic criteria are:

- Abrupt, dramatic onset of OCD or severely restricted food intake.
- Concurrent presence of additional neuropsychiatric symptoms, with similarly severe and acute onset, from at least two of the following seven categories:
 1. Anxiety
 2. Emotional lability and/or depression
 3. Irritability, aggression and/or severely oppositional behaviors
 4. Behavioral (developmental) regression
 5. Deterioration in school performance
 6. Sensory or motor abnormalities
 7. Somatic signs and symptoms, including sleep disturbances, enuresis or urinary frequency.
- Symptoms are not better explained by a known neurologic or medical disorder, such as Sydenham's chorea, systemic lupus erythematosus, Tourette disorder or others.

When the symptoms are considered to be secondary to a preceding group A streptococcal (GAS) infection, the term **pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection** (PANDAS) is often applied. An initial autoimmune reaction to a GAS infection is thought to produce antibodies that continue to interfere with basal ganglia function, causing symptom exacerbations. The hypothesis remains controversial.

CHILD ABUSE AND NEGLECT (NON ACCIDENTAL INJURY, BATTERED BABY SYNDROME, CHILD MALTREATMENT)

The term refers to maltreatment (physical, sexual or emotional) of children by the parents, guardians or other caretakers. Abuse is an act of commission on the part of parents or caretakers. Neglect is an act of omission on their part.

Almost 75% of the child abuse and neglect (CAN) recognized in hospitals are physical, 20% sexual and 5% emotional/nutritional deprivation leading to non-organic failure to thrive.

ETIOLOGY

Battering is generally encountered in unhappy homes. These families have gross stresses such as monetary instability, unwanted pregnancy, arrival of a more precious newborn and mental illness. The last named applies to both, parents as well as babies. The latter may be mentally-retarded social rejects.

A substantial proportion of the parents who batter their children are the ones who had experienced physical or other abuse as children. They are neither criminals nor psychopaths, but just unhappy adults living under tremendous stress and strain.

The child most likely to be battered has the following predispositions:

- Negativism
- Difficult temperament

- Enuresis
- Soiling
- Habitual crying
- Spilling
- Mental subnormality.

It has been suggested that child labor should be regarded as a form of child abuse.

A peculiar form of CAN, the so-called **Munchausen syndrome** by proxy, is characterized by a fabricated or falsified illness courtesy one of the parents, usually the mother who is connected with the medical profession (say a nurse). The following 4 criteria must be satisfied for this diagnosis:

1. Illness in a child is fabricated by a parent.
2. The child is presented for medical assessment and care, usually persistently, often resulting in a multitude of medical procedures.
3. The perpetrator denies the etiology of the child's illness.
4. Acute manifestations of illness disappear when the child is separated from the perpetrator, invariably the mother.

Notably in a family where parental behavior of fabricating illness is evident, the risk of a variety of abuses and neglect in the siblings is high.

CLINICAL FEATURES

Physical Abuse

Usually a battered baby is less than one year of age, sometime less than four years, but uncommonly beyond this age.

He is brought with painful swellings, restriction of movements and some contusions over areas corresponding to the ends of the long bones. The arms may reveal finger and thumb impressions of the abuser. Thrashing with a belt, stick or ruler may leave lash marks on the body. Bite marks are seen as crescent-shaped bruises. Slap marks are seen as two or three parallel bruises, usually over the cheeks. The neck may reveal choke marks. Strings or ropes tied around ankle or wrists leave circumscribed marks. The presence of black eye and contusions over face or sides of the head often clicks the diagnosis.

Burn marks (Fig. 6.1) may be characteristic of the modus operandi. Punched out circular lesions of nearly the same size suggest cigarette burns. A circular type of burn involving only the buttocks or thighs and waist point to hot water injury.

Physical abuse may result in as dangerous an injury as subdural hematoma, manifesting with convulsions and coma. A blow injury over the abdomen may cause tearing/rupturing of liver or spleen.

Clinical manifestations out of proportion and/or in discrepancy with parent's story, abnormal attitude of parents and a gap of some days between onset of symptoms and signs and parents seeking medical advice should arouse suspicion.



Fig. 6.1: CAN: Note the old scalds of burns inflicted by battering father in a mentally challenged girl.

Sexual Abuse

Molestation, intercourse and rape are the three types of sexual abuse seen in practice. Skin, mouth, rectum and external genitalia may show evidence of trauma. A hymenal opening of over 5 mm should be considered abnormal in a prepubertal girl. Pedophilia refers to sexual abuse (attack) on children less than 10 years of age.

Non-organic failure to thrive

An unwanted child may be deprived of emotional stimulus and/or nutrition. Manifestations include signs of nutritional deficiencies, and stark hygienic neglect (nappy rash, impetigo, scabies, unwashed skin, uncut nails, dirty clothing).

DIAGNOSIS

Physical Abuse

Whenever battering is suspected a complete radiologic survey of the skeleton should be done. Soon after injury, X-ray shows soft tissue swelling and detachment of thin bone fragments from the metaphysis. Deposition of new bone in and beneath stripped periosteum in several days may lead to visible hyperostosis. At times, direct injury of epiphyseal cartilage can cause shortening of shaft with cupping of the shortened end. Linear fractures of skull and fractures of ribs may also be present. Subdural hematoma is found in some cases. In such cases, presence of retinal hemorrhages should be looked for. Retinal hemorrhages are a marker of abusive head trauma (AHT) as a result of violent shaking, asphyxia or direct impact.

Differential diagnosis is from scurvy, leukemia, Caffey disease, suppurative arthritis, congenital syphilis, osteogenesis imperfecta, etc. Lack of familiarity with CAN may lead to initiation of irrelevant, unnecessary and expensive investigations.

112 Sexual Abuse

Since there may be no definite physical evidence of sexual abuse, physician should employ dolls and pictures to clarify body parts and to build up the story rung by rung.

Non-organic Failure to Thrive

Dramatic improvement following hospitalization and feeding trial establishes the diagnosis.

TREATMENT

Child battering always indicates serious underlying family disturbances. Clinical manifestations out of proportion and/or in discrepancy with the parent's story, an abnormal attitude of parents should arouse suspicion. The handling of the problem needs assistance from a psychiatrist, a social worker and sometimes the police. It is a must to hospitalize such a child, not for sheer diagnosis, but for his safety as well. Infrequently, the abused child may need to be permanently kept away from his home if parents are guilty of dangerous aggressive tendencies.

PROGNOSIS

Maltreated and abused children may suffer from emotional problems such as fearfulness, low self-esteem, juvenile delinquency, substance abuse, hyperactivity, aggression, denial, lack of trust, projection and hypervigilance, etc. In the long run, they may end up as delinquent, violent, antisocial adults and potential child abusers.

PREVENTION

Pediatricians need to take a proactive role towards prevention of CAN and promotion of child welfare. Similar responsibility also lies on the civil society.

MUNCHAUSEN SYNDROME BY PROXY (Factitious Disorder by Proxy)

It is also called factitious illness, Munchausen syndrome by proxy (MSBP) is a situation in which an adult, usually the mother, simulates manifestations of a disease in the child or causes symptoms through exposure to a toxin or drug, or alter laboratory samples/reports or temperature record. When an adult falsifies his own symptoms of an illness, the term, *Munchausen syndrome* is employed.

Clinical Features

- Bleeding (hematuria, dysentery), fever, seizures, apnea, vomiting, diarrhea, skin lesions, etc., are the common complaints for which the care-taker approaches the health facility.
- Infrequently, life-threatening actions (partial strangulation) by the offending care-giver may be there.

Etiology

Interestingly, there is no specific motive for doing so—at least not at the conscious level—which contrasts it from malingering in which a definite motive exists and the subject himself rather than other individual fabricates illness symptoms.

The characteristics of the offending care-taker, usually the mother, include:

- Connected with the medical profession.
- Unaccompanied by child's father during visits.
- Demonstration of much-too-much concern for the child despite little emotional attachment.
- Often having a history suggestive of Munchausen syndrome.
- Often, it is she rather than the doctor who has suggested the test(s).
- Repetition of the problems time and again over years.

Diagnosis

A high index of suspicion together with presenting complaints that is not in keeping with a recognizable disease, and tracing details of previous medical records to assist in arriving at the diagnosis. A hidden video camera may be of considerable help in detecting the condition.

Management

Assuming that a psychiatric problem may be the underlying cause, psychotherapy is indicated for the offending care-taker. In case of a serious threat to the child, he may need to be separated from the offending parent and given protection.

ROLE OF PEDIATRICIAN IN BEHAVIORAL, DEVELOPMENTAL AND PSYCHIATRIC DISORDERS

Under ideal conditions, *Child Guidance Clinic* (Box 6.8) is the best place for arriving at the exact diagnosis and management of behavioral, developmental, psychological and psychiatric disorders in children.

Box 6.8 Child guidance clinic

Definition

CGC is defined as a center where children with developmental, behavioral (including adjustment) and psychiatric disorders are provided guidance and therapy in a holistic manner.

Multidisciplinary team

A psychiatrist, a pediatrician, a public health nurse, and educational psychiatric social worker, and playroom workers, form the team.

Assessment and therapeutic approach

The child is treated as a whole. Since child's personality has many such aspects as , physical, intellectual, educational, emotional, social and economical, specialist team members study each of these aspects. By working together, interaction and discussions, they formulate a plan of management with the aim of reintegrating the personality and bring about lasting benefit to the child as well as the family.

Components of Management

• Treatment of the child

- Treatment of any physical illness if it is present.
- Psychotherapy: Suggestion and Persuasion, Hypnosis, Re-education (d) psychoanalysis
- Play therapy and other forms of expressive therapies
- Change of environment as treatment. (a) Foster home placement (b) Institutional placement (c) School's part in changing the child's behavior

• Family attitudes as a focus of treatment

- Attitude therapy to the parents.
- Treatment of psychoneurosis or psychosis in parents, if and when necessary.

But, such facilities may not be available to most of the emotionally disturbed children in low-income settings. It is, therefore, desirable that pediatricians (in fact all doctors dealing with children) should have a working knowledge pertaining to identification and handling of the emotional, behavioral and developmental disorders of childhood. Its knowledge in case of a pediatrician is of particular importance, at least for two reasons.

- First, his first contact with the child and his parents and the subsequent contacts uniquely contribute to evaluating the development of the child and advising the parents about his upbringing.
- Secondly, it is vital for him to identify psychosocial or psychotic problems not only for managing these but also for seeking psychiatric consultations as and when indicated. Symptoms in childhood psychiatric

disorders are subtle and are likely to be passed off as normal variants. Even in frank cases, parents are reluctant to consult a psychiatrist due to social taboos.

The field of child psychiatry helps pediatrician to understand the child through and through as a living, acting, feeling, and choosing being. Nevertheless, he is unlikely to fulfill this function completely and earnestly without the knowledge of fundamentals of psychosomatic disorders.

The best way to treat a child with psychosomatic problem is to have an understanding of his family and interaction between him and the significant persons connected with him. Though child is treated through psychotherapy and play-therapy, his parents must actively participate in the management. In fact, in many instances, it is the parental end that is in real need of counseling. Pediatrician is the best person to motivate parents for this.

Multiple Choice Questions

1. Most frequent cause of enuresis is:
 - A. Urinary tract infection
 - B. Psychological stress
 - C. Diabetes mellitus
 - D. Spina bifida
2. Multiple fractures at various stages of healing are characteristic of:
 - A. Child abuse
 - B. Achondroplasia
 - C. Scurvy
 - D. Rickets
3. Which of the following is not a recommended therapy for nocturnal enuresis?
 - A. Imipramine
 - B. Desmopressin
 - C. Dexedrine
 - D. Behavioral therapy
4. Spot the wrong observation:
 - A. Discrepancy between potential (ability, IQ) and achievement, resulting in underachievement, especially in reading, is the most important clue to developmental delay
 - B. DSM-5 has revised the diagnosis of different types of learning disabilities into a single category, specific learning disorder
 - C. Least common ADHD is Class I, i.e. hyperactivity, impulsiveness and inattentiveness
 - D. Atomoxetine, a non-stimulant agent, has been recommended as a preferred drug for adolescent ADHD and ADHD with comorbidities and contraindications to stimulants
5. Incorrect statement about autistic spectrum disorder is:
 - A. MMR vaccine must not be given to these children
 - B. Presence of functional speech and good IQ favors better prognosis
 - C. Under ASD umbrella are now included all pervasive disorders except Rett syndrome
 - D. Methylphenidate is useful for ASD with disruptive behavior
6. Which of the following, according to DSM criteria is a symptom of hyperactivity/impulsivity?
 - A. Does not seem to listen when spoken to
 - B. Does not finish school work
 - C. Blurts out the answer before his turn
 - D. Often loses things
7. In which of the following categories of childhood behavioural problems will you consider the problem of breath-holding?
 - A. Habit problems
 - B. Eating disorders
 - C. Sleep problems
 - D. Speech problems

contd...

8. By what age does, in years, does a child begin indicating bowel bladder fullness?
- One and half
 - Two
 - Two and half
 - Three

Answers

- | | | | | | |
|------|------|------|------|------|------|
| 1. B | 2. A | 3. C | 4. C | 5. A | 6. C |
| 7. A | 8. C | | | | |

Clinical Problem-solving

Review 1

SK, a 16-year-old boy, is quite intelligent, a good painter and a good sportsperson having a bagful of prizes to his credit. Yet, he has failed in his matric exams twice. His ophthalmic and ENT checkups are normal. The class teachers raise fingers to his reading, writing and spelling problems for his poor academic performance.

- What can be his problem of academic achievements falling so behind his overall status?
- How to arrive at the diagnosis?
- What can be done for this disorder?
- Any vocational course for such children?

Review 2

A 3-year-old daughter of a nursing orderly, has been brought to a pediatrician for the fourth time for "blood in urine" in a few months timespan. Clinically, she is perfectly normal. All relevant investigations are normal, except "10–12 RBCs/HPF".

- What could be the cause of unexplained hematuria?
- How to resolve this diagnostic dilemma?
- Is it a sort of malingering?

Review 3

A 1-year-old infant is brought with what parents believe to be "recurrent seizures". There is a history of parents report crying followed by duskiness of face followed by stiffening of the entire body. Parents have witnessed at least 3 such episodes in the last 2 months. This is the first child in a joint family.

- What is the most likely diagnosis?
- Will you use an antiepileptic drug in this child?
- Any comorbid conditions you should look for/treat?

Answers**Review 1**

- Academic achievement not in keeping with overall potentials in extracurriculars certainly arouses the possibility of a specific learning disability, precisely dyslexia.
- In order to test speed, accuracy and comprehension in reading, writing and spelling, certain special tests can be conducted.
- A multidisciplinary approach, involving the class teacher, remedial teacher, parents, social worker, pediatrician, psychologist and, if warranted, even a psychiatrist, is important in managing the learning disability.
- National Institute of Open Schooling offers a wide selection of vocational and non-vocational subjects upto pre-degree level to circumvent the difficulties of these children. No paper is compulsory.

Review 2

- Repeated episodes of hematuria not justified by any organic condition should arouse suspicion of Mauchasen syndrome by proxy. In this condition, a caretaker (usually the mother) feigns blood in child's urine (or perhaps something different).
- The so-called "blood in urine" may well be a coloring agent or, sometime, actual blood added to child's urine. In the latter case, blood group testing can resolve the diagnostic dilemma.
- No, it is neither malingering nor hysterical conversion reaction. The problem is not with the child. It is with the caretaker who invariably suffers from a psychiatric illness.

Review 3

- The most likely diagnosis in this infant is breathholding spells. The description of the event starting with crying followed by duskiness indicates a cyanotic breath-holding spell. Prolonged hypoxia may lead to the abnormal stiffening of the body.

contd...

2. No antiepileptic drugs are recommended.
The abnormal stiffening may follow a prolonged episode of breath-holding and one must differentiate it from a true seizure. An EEG may be done if a seizure is strongly suspected, to rule out or confirm the same.
3. One must look for anemia as it is commonly correlated with the occurrence of breath holding spells and can be an aggravating comorbidity. Secondly, one must address the family and their behaviors which may be contributing to frequent episodes. In this case being the only child in a joint family may be a cause for over concern, overprotection and overindulgence. All this may contribute to development of behavioral problems in the child.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

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1. Greydanus DE, Pratt HD. *Attention Deficit Hyperactivity Disorder*. In: Greydanus DE, Patel DR, Pratt HD (eds): *Behavioral Pediatrics*, 2nd edn. New York: Universe 2006.
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OVERVIEW

By definition, adolescence is the phase, usually between 10–20 years, in which children undergo rapid changes in body size, physiology, psychological and social functioning. All body dimensions, development and maturation are completed. This is the net result of hormones and social structures designed to foster the transition from childhood to adulthood.

It is with the onset of puberty that adolescence begins. United Nations Children's Fund (UNICEF) defines puberty as—the sequence of events by which individual is transformed into a young adult by a series of biological changes. It is during this period that secondary sex characteristics develop. These sex characteristics have been rated into five stages by Tanner and termed **Tanner's sexual maturity rating (SMR)**. Globally, a secular trend is being noticed towards earlier puberty. What indeed constitutes end of puberty remains controversial. Arbitrarily, adolescence is divided into three phases:

1. **Early adolescence:** Age 10–13 years.
2. **Middle adolescence:** Age 14–16 years.
3. **Late adolescence:** Age 17–20 years.

Until recently, the adolescent remained neglected by the medical profession as neither the physicians for adults nor the pediatricians looked after his problems. He, in actuality, appeared to be no one's responsibility, especially in India and other source limited countries. Recently, of course, thanks to the concerted efforts of the World Health Organization (WHO) and the UNICEF, a worldwide campaign has begun to focus attention on adolescence.

Back home in India, for example, the Indian Academy of Pediatrics (IAP) took lead in focusing attention on adolescence by declaring the year **2000** as the **IAP year of the adolescent** and the **August 1** every year as the **teenager day**. According to the IAP, health problems of children upto 18 years (inclusive) should be the responsibility of pediatricians. The 2013 IAP launched initiative, **Mission Kishore Uday**, address the health needs of the adolescents in India.

- In United States of America, pediatrics includes individuals upto the age of 21 years.
- UNICEF is contented with **upto 18 years** as the pediatric age group.
- According to the WHO, adolescence is the period of life that extends from 10 years to 19 years.
- The IAP defines adolescence as the period of life between 10 and 18 years (inclusive).

All these definitions may be all right for statistical convenience rather than for biological accuracy.

SPECIAL FEATURES OF THREE PHASES OF ADOLESCENCE

1. **Early adolescence (10–13 years):** Growth spurt and secondary sex characters.
2. **Mid adolescence (14–16 years):** Separate identity from parents, new rapport with peer groups and opposite sex and experimentation.
3. **Late adolescence (17–20 years):** Established adult physical characters, distinct identity and opinions and ideas.

Developmental characteristic of three phases of adolescence are summarized in Table 7.1.

PUBERTY CHANGES (Changes During Adolescence)

Morphological Changes

Morphological changes revolve a round rapid and final growth spurt and development of secondary sex characters.

Order of Morphological Changes in Girls

- Accelerated gain in weight and height
- Breast changes like pigmentation of areola and enlargement of breast tissue and nipple
- Increase in pelvic girth
- Appearance of pubic hair
- Activity of axillary sweat glands
- Appearance of axillary hair
- Onset of menstruation (menarche). The first bleed occurs usually two years after the first manifestation of puberty
- Abrupt slowing of gain in height.

Order of Morphological Changes in Boys

- Accelerated gain in weight and height
- Enlargement of external genitalia
- Appearance of pubic hair followed by hair in axilla, upper lip, groin, thigh, and between pubis and umbilicus. Facial hair appear about two years after the pubic hair
- Changes in voice
- Nocturnal discharge of seminal fluid
- Abrupt slowing in gain in height.

TANNER'S SEXUAL MATURITY RATING

This quantifies sexual growth from 1 to 5 which is listed in Table 7.2. In case of boys, genitalia and pubic hair and in case of girls genitalia and breasts are of prime

Table 7.1: Developmental characteristics of three phases of adolescence

Characteristics	Early adolescence	Middle adolescence	Late adolescence
Age (years)	10–13	14–16	17–20
SMR	1–2	3–5	5
Somatic development	Secondary sex characters, onset of rapid growth, awkward	Height growth peaks, body shape and configuration changes, acne appears, menarche, spermarche	Slower growth
Sexual development	Sexual interest much more than sexual activity	Sexual drive surges, experimentation, questions of sexual orientation	Consolidation of sexual identity
Cognitive and motor absolutism development	Concrete operations, conventional morality	Appearance of abstract thoughts, self-centered, questioning more	Idealism
Self-concept	Preoccupation with changing body, self-conscious	Concern with attractiveness, increasing introspection	Relatively stable body image
Family independence, secure base	Struggles for greater independence	Struggles for acceptance of greater autonomy	Practical family remains
Peers possicommitment	Same sex groups, conformity, cliques	Dating, peer group less important	Intimacy
Relationship to society	Middle-school adjustment	Gauging skills and opportunities	Career decisions (dropout college, work)

Abbreviation: SMR, sexual maturity rating.

Table 7.2: Tanners sexual maturity rating**Pubic hair (PH) stages for boys and girls**

- **PH-1:** Preadolescent, no pubic hair.
- **PH-2:** Sparse growth of long, pigmented hair at base of penis (boys) and bilaterally along medical border of labia (girls).
- **PH-3:** Hair, which begin to curl and develop increased pigmentation, spread laterally in boys and over mons pubis in girl.
- **PH-4:** Hair become coarse and involve more area.
- **PH-5:** Hair spread to medical side of thigh.

Genitalia (G) stages for boys

- **G-1:** Testes, scrotum and penis of small size.
- **G-2:** Testes and penis slightly enlarged, scrotum develops red hue.
- **G-3:** Testes, scrotum and penis further enlarge.
- **G-4:** Penis enlarged in breadth and develop, glans, scrotal skin become dark.
- **G-5:** Mature adult sized scrotum, testes* and penis.

Breast (B) development stages in girls

- **B-1:** Pre-adolescent, elevated papilla.
- **B-2:** Breast bud forms, elevated breast and papilla, increased areolar diameter.
- **B-3:** Further enlargement of breast and areola without separation of the contours.
- **B-4:** Well-defined breast contour with areola and papilla forming a secondary mound above the concur.
- **B-5:** Mature breast with areola receding into general contour of breast and papilla projecting as nipple.

* The objective tool for measuring size of testis (over and above the conventional clinical palpation) is Prader's orchidometer.

considerations (Figs 7.1 and 7.2). No sexual growth (pre-pubescent stage) means SMR-1 whereas full sexual growth means SMR-5.

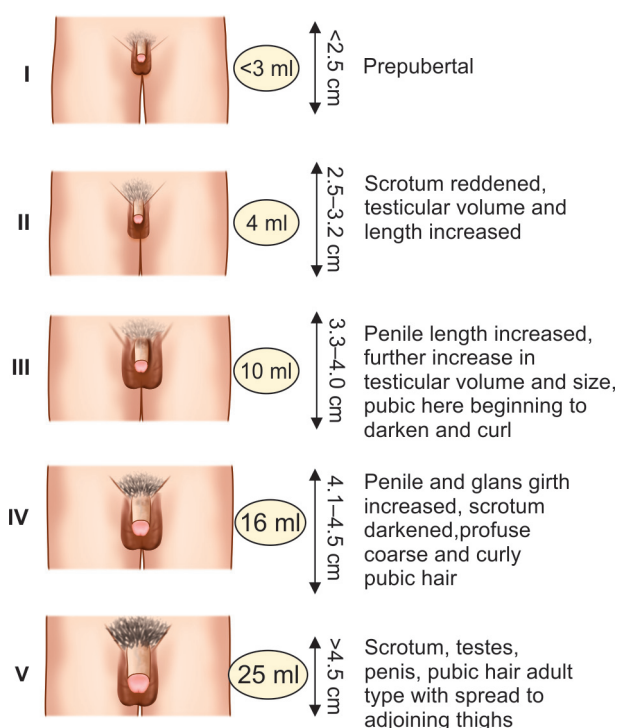


Fig. 7.1: Tanner's sexual maturity rating (SMR 1–5) in boys.

Puberty Spurt

This is a remarkable feature of puberty. As much as 50% of the adult weight and 25% of the adult height are attained during this period of life. No doubt, there is a wide variation in the age of onset as also the rate of puberty spurt. Major weight gain in boys is because of dominant muscular development. In girls, fat deposition in characteristic female distribution is responsible for it. Box 7.1 summarizes the three phases of growth spurt.

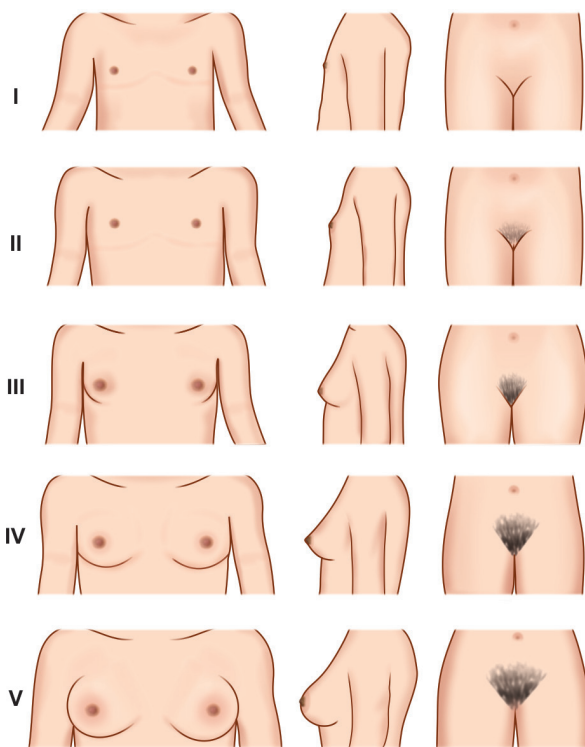


Fig. 7.2: Tanner's sexual maturity rating (SMR 1–5) in girls.

Psychological Changes

Psychological changes include development of:

- Identity different from parents
- Self-esteem
- New relationship with peer groups, opposite sex, community
- Exploration of own and other's bodies as also potentials, and
- Experimentation with risks such as speedy driving, drug abuse, particularly under influence of electronic and other media and peers
- Anxiety related to wet dreams causing night discharge in boys and delayed menses or vaginal discharge in girls may cause nonspecific neurotic manifestations such as intractable headache, abdominal pain, sleeplessness and lack of concentration
- Body image concerns (height, weight, muscles, complexion, facial features, hair, acne, breast size) may cause such problems as:
 - Bulimia, anorexia nervosa
 - Inferiority complex
 - Depression
 - Withdrawal
 - Jealousy
 - Undue argumentation
 - Deterioration in day-to-day functioning and studies.
- Disturbed relationship with family members and peers may suffer.

Most body image concerns are invariably an outcome of distorted perceptions rather than reality. More details follow under the heading "Adolescent Psychology" in this very chapter.

Box 7.1 Three phases of puberty growth spurt

1. **Phase 1:** Moderate gain in height velocity in the pre-pubescent phase.
2. **Phase 2:** Both height and weight show rapid gain in the pubescent phase.
3. **Phase 3:** Growth velocity shows deceleration though weight gain continues in the post-pubescent phase.

FACTORS INFLUENCING ADOLESCENT HEALTH AND DEVELOPMENT

Modifiable (External) Factors

Protective Factors

- Positive family environment—caring and meaningful relationship with family and neighborhood
 - Positive school environment
 - Encouragement for self-expression
 - Opportunities for participation and contribution
 - Structure and boundaries for behaviors
 - Spiritual belief.
- These protective factors:
- Encourage and sustain positive behavior
 - Reduce risk of negative health behavior and outcomes
 - Support recovery from negative health outcomes.

Social, Cultural and Political Factors

- Social norms and attitudes
- Relationship with family, friends and teachers
- Interaction with peer groups
- Mass media
- Government policies.

Gender-related Factors

- Greater attention, better nutrition, preferential treatment, more opportunities and resources for boys at the expense of girls.
- Insufficient attention to boys as regards with reproductive health and contraceptive use.
- Encouragement to boys for risk behavior, resulting in injury and violence.

Non-modifiable (Internal) Factors

Age and sex are among those factors that cannot be modified.

ADOLESCENT PSYCHOLOGY

Self-esteem (Self-concept)

The adolescent's personal evaluation or view of self influences his feelings and behavior. It is the result of an interaction between the adolescent's temperament and the environmental influences and considerably contributes to motivation and performance, peer relationship, failure or success and ability to bounce back from a failure. Any sort of a conflict in the development of an adequate self-esteem may cause one or more psychological problems.

Formation of the Identity

Physical maturation, joining the peer group and heterosexual relationship are the hallmark of early adolescence.

The middle and late adolescence is characterized by autonomy from parents, sex role identity, morality and career choice. Failure to accomplish these tasks may cause psychological problems.

A vital feature of middle adolescence is tendency to join a peer group and endeavor to win popularity among friends circle. At the same time, the adolescent moves away from parents, challenges their authority and, as a result, frequently gets into a conflict with them. In case parents are understanding and accommodating, the adolescent usually tides over this phase and adapts to the situation.

The conflicts and pressures may contribute to such problems as depression, suicide or suicidal attempt, school problems (school phobia, failures) and juvenile delinquency.

Psychological Problems

Adolescent psychological problems may fall in one of the following three categories:

1. **Emotional**, which include anxiety, hypersensitivity, impulsiveness, moodiness, immaturity, withdrawal, etc.
2. **Motivational**, which include lack of ambition, low aspirational level, feelings of frustration, negative attitudes, lack of interests, etc.
3. **Moral**, which include feelings of guilt, sense of being lost, confused ideas of right and wrong, delinquencies such as lying, stealing and unruly behavior, etc.

ADOLESCENT SEXUALITY

Though an adolescent is still a child, he is almost an adult as far as physiological and sexual maturation is concerned as a result of hormonal changes. No doubt, this sudden transformation together with exposure to influences of peers and print and electronic media leaves him utterly confused on his knowledge, attitudes and behavior concerning sex.

Sexual Concerns

The adolescent is often anxious about nocturnal discharge, penile size, shape and erection, growth of hair, menses, breasts, and appearance to influence the opposite sex. The usual barrier of communication with the parents enhances adolescent's worry.

Self-gratification

Most adolescents indulge in self-gratification (masturbation) to quench their sexual desire and obtain pleasure out of this practice. Yet, they are left with an intense feeling of guilt and run about foolishly to get treatment for this harmless practice from quacks and other unscrupulous elements.

Homosexuality

Sooner or later, the adolescent may develop a very intimate closeness with an individual of the same sex. As a rule this is a transitional phase in an adolescent's life and in due course dies down. However, in a small proportion of the adolescents, such a homosexual relationship may pass on

into adult life on account of an enhanced fixed identity, leading to problems. **119**

Promiscuous Sex

Aging the West is usual in the developing countries such as India. Understandably, therefore, the promiscuity in adolescents is on an increase. This is not restricted to peer groups.

Quite a proportion of adolescents mates with prostitutes. A large majority of these are sexually active, but ignorant. Paradoxically, adolescents seldom use any contraceptive measure such as condoms, thereby exposing themselves to unsafe (unprotected) sex, resulting in sexually transmitted diseases (STDs) and unwanted pregnancies, illegal abortions with complications, maternal deaths, abandoned babies and, no doubt, population explosion.

Adolescents must not grow up with beliefs and notions that are dangerous for the future sex life. They need to protect themselves from sexual abuse and exploitation.

To achieve this goal, sex education, in a well-conceptualized way, should be given in schools by the specially trained teachers. If need be, help from doctors, psychologists/psychiatrists and sexologists may also be sought for this purpose.

We must empower children with knowledge and information so that they may fight the cancer of untruths with confidence. The argument by the cynics that burdening children's minds with what is essentially the task of the adults seems by and large unfounded.

ADOLESCENT NUTRITION

On account of a rapid gain in height and weight, nutritional requirements, including calories, proteins and micro-nutrients such as iron, calcium, zinc, folic acid and iodine, are at peak during adolescence (Table 7.3). The adolescents who participate in athletics and sports are in need of a higher intake of proteins as well as calories. Similarly, nutritional requirements of a pregnant adolescent are relatively much higher (Table 7.4). Risk for undernutrition and micronutrient deficiency is, therefore, increased during this period. In adolescent girls in particular, importance of nutrition is remarkable since the growth and development of infants is dictated by their mother's past nutritional status.

The adolescent is particularly vulnerable to certain peculiar eating disorders on account of hormonal and psychological changes, say anorexia nervosa, bulimia, and obesity which are discussed later in this very chapter.

In addition, fast food, junk food and snacking, which is fast becoming the order of the day, especially in urban adolescents, but is imbalance, may contribute to overweight and obesity plus nutritional deficiency states.

The economically deprived children suffer from nutritional deprivation which they carry over to adolescence with physical and, at times, intellectual deficit limits their productivity. The stunted and malnourished adolescent girls are particularly at a high risk of producing low birth weight (LBW) babies when they become mothers.

Table 7.3: Nutritional requirements of Indian adolescents as per recommendations of the Indian Council of Medical Research (ICMR)

Age groups (years)	Weight (kg)	Calories (kcal)	Protein (gm)	Calcium (mg)	Phosphorous (mg)	Iron (mg)	Zinc (mg)	Iodine (µg)	Folic acid (µg)	Vitamin A (µg)
10–12										
Boys	35.54	2194	51.9	600	600	34.2	15	150	100	600
Girls	37.91	1965	55	600	600	18.9	15	150	100	600
13–15										
Boys	47.88	2447	67	600	600	41.4	15	150	100	600
Girls	46.66	2056	62.1	600	600	28	15	150	100	600
16–18										
Boys	57.28	2642	75.1	500	500	49.5	15	150	100	600
Girls	49.92	2064	60.4	500	500	29.9	15	150	100	600

Table 7.4: Recommended dietary allowances for pregnant adolescents

	11–14 years	15–18 years
Energy (kcal/day)	Extra 500	Extra 400
Protein (g)	1.7 g/kg	1.5 g/kg
Vitamin A (µg)	800	800
Vitamin D (µg)	15	15
Vitamin C (mg)	60	70
Thiamine (mg)	1.5	1.5
Riboflavin (mg)	1.6	1.6
Niacin (mg)	17	17
Vit B ₆ (mg)	2.0	2.1
Folate (ng)	370	400
Vit B ₁₂ (mg)	2.2	2.2
Calcium (mg)	1600	1600
Iron (mg)	30	30
Zinc (mg)	15	15
Iodine (µg)	175	175

Note: Requirements in addition to those of age matched non-pregnant women.

SPECIAL HEALTH, MEDICAL AND PSYCHOSOCIAL PROBLEMS OF THE ADOLESCENTS

Infections

In addition to tuberculosis, skin infections, fungal infections and parasitosis, adolescents are particularly vulnerable to human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), hepatitis B, STDs such as gonorrhea, trichomoniasis, candidiasis, genital warts, herpes, chlamydia, and primary syphilis because of early sexual activity without barrier contraceptives.

In sexually active girls, pelvic inflammatory disease (PID), manifesting as abdominal discomfort/pain and vaginal discharge, may occur.

Even scabies and pediculosis are common in adolescents from down-trodden background. Proper health education as a preventive measure against such infections is of critical importance.

Eating Disorders

Anorexia Nervosa

In a pursuit for *slimness* and *weight loss*, many adolescents (by and large, girls), impose foolish dietetic restrictions on themselves (anorexia nervosa of restricting type) or eat in binges and then get rid of the food intake by self-induced vomiting or using cathartics, i.e. bulimia (non-restricting, purging or binge eating type). As a result, they become grossly malnourished. Disturbances related to almost all organ systems, i.e. electrolyte disturbances, postural hypotension, cardiac arrhythmias, heart failure, hypothermia, amenorrhea, constipation, dry skin with lanugo hair, peripheral edema, rise in blood urea nitrogen (BUN) and bone marrow hypoplasia, etc. also crop up. Interestingly, the subjects are more or less resistant to infection.

The exact etiology is unclear. However, it is generally believed to be a psychiatric eating disorder. The patients have characteristics such as developmental immaturity, isolation and excessive dependence. The family background is overprotective.

Bulimia Nervosa

It is characterized by recurrent episodes of rapid consumption of a large amount of food in a discrete period of time (binge eating) as a result of lack of control over eating behavior. The subject regularly engages in self-induced vomiting, use of laxatives or diuretics, strict dieting or fasting, or vigorous exercise in order to prevent weight gain. These adolescents are obsessed with persistent over concern with body shape and weight.

Binge Eating Disorder

Central to bulimia is the binge eating behavior which is characterized by eating in a discrete period of time (say,



Fig. 7.3: Binge eating. The adolescent indulges in eating in a discrete period of time (say, within any 2 hour period) an amount that is very large.

within any 2 hour period); an amount that is certainly larger than most adolescents would eat in a similar period of time under similar circumstances (Fig. 7.3). There is a sense of lack of control over excessive eating during the episode. Use of inappropriate compensatory behaviors in the form of purging, fasting, excessive exercise, etc. is not a feature of this disorder. Also, *See* Chapter 5 (Development).

Management revolves around psychotherapy (including pharmacotherapy with antidepressant agents), behavior modification and nutritional rehabilitation.

Malnutrition

Nutritional needs during adolescence are considerably enhanced as a result of hike in growth during these years. Unless and until they are provided extra calories, proteins, vitamins and minerals in diet to meet the increased demands for rapid gain in weight and height, they run the risk of developing nutritional deficiency states, including vitamin and mineral deficiencies.

Consequent upon nutritional deficiency states, delay occurs in onset of puberty and sexual maturation. Moreover, they run the risk of stunting.

Iron Deficiency Anemia (IDA)

Adolescents are likely to develop IDA because of increased demands. In girls, an important additional factor is excessive loss of blood in menses. According to National Family Health Survey (NFHS), over 50% of adolescent girls in India are anemic.

It is, therefore, advisable to provide adolescents, especially girls, supplements of medicinal iron/folate, preferably with vitamin C. A public health approach comprising once weekly distribution of iron-folic acid supplementation (preferably with vitamin C) through schools and welfare centers is a desirable strategy.

Obesity

An adolescent is particularly prone to develop obesity. A multiplicity of factors, including growth spurt, hormonal changes, erroneous eating habits (say excessive consumption of ice-cream, candies, chocolates, and sweets), exces-

sive television viewing, lack of outdoor activity, etc. join hand to contribute to it.

In adolescent girls, obesity may be a feature of polycystic ovary syndrome which is characterized by menstrual irregularities, ovarian cysts and excess of androgens. The latter causes symptoms such as excessive growth of facial hair (hirsutism) and acne.

Comorbidities of obesity include:

- Psychological problems such as low self-esteem which further force them to turn to more food and isolation, causing further obesity
- Lifestyle diseases such as diabetes, cardiovascular disease and systemic hypertension
- Fatty liver, nonalcoholic cirrhosis
- Gallstones
- Asthma
- Sleep disorders
- Gastroesophageal reflux disease (GERD)
- Slipped femoral epiphysis
- Tibia vara (Blount disease).

Management revolves around rational reduction in intake of calories and hike in physical activity. The pharmacotherapy aimed at suppressing appetite should be avoided.

Puberty Goiter

Puberty goiter is a common problem of the adolescents, especially the girls. Usually, it subsides in due course of time. However, at times, it may become much larger in size and multinodular. It should be treated with thyroid hormone.

Depression

Adolescence is a period of mood swings varying from depths of depression to heights of elation. This should be considered normal.

- **Acute depressive reactions** are a sort of healthy grief response following death or separation from a loved one. These resolve in due course of time, occasionally after weeks or months.
- **Neurotic depressive disorders** are unresolved grief reaction and are characterized by a feeling of guilt in relationship to the dead. A psychiatric treatment is in order.
- **Masked depression** is characterized by denial and somatization of feelings of despair, hopelessness and helplessness by the adolescent. Manifestations include acting-out behavior in the form of substance abuse, school truancy, running away from home, multiple accidents, unexplained headache, abdominal pain, etc. A psychiatric treatment is mandatory.
- **Psychotic depressive disorders** may have additional manifestations such as delusions of guilt, impaired reality testing and thought distortion. Psychiatric treatment is strongly indicated.

Suicide

Suicide is one of the important causes of deaths among adolescents. Its causes include serious conflicts and

122 pressures, successive failures in examination, marriage against will, chronic illnesses causing fear of fatality, impotence, diminished competence, poor self-image, vulnerability to loss of a loved one and increased access to medication that could facilitate suicide.

Most successful suicides are known to have occurred in individuals who have threatened ending life or who have made earlier attempts or gestures. Secondly, threats of suicide must never be taken casually, especially if the person leaves a suicide note, a sign of seriousness and premeditation. A family history of suicide is significant.

Among the methods of suicide figure ingestion of medication such as phenobarbital or tricyclic antidepressants in very large amounts, hanging, setting fire to one's personnel, drowning, shooting or slashing one's neck or wrist.

Any suicidal attempt is an indication for a psychiatric evaluation and management. A short-term hospitalization is of distinct value in providing a secure environment to the subject and helps the individual in the constructive resolution of his conflict.

Substance Abuse

The menace of substance abuse (illicit drugs, alcohol, tobacco, etc.) has not spared the adolescents in the low-income world too (Fig. 7.4). Such is the magnitude of the problem that it has been suggested that each and every adolescent should be assessed for drug abuse and its physical and functional adverse effects.

Among the drugs abused by adolescents figure central nervous system (CNS) stimulants (dextedrine, methedrine), CNS depressants (opiates), hallucinogens (Lysergic acid diethylamide {LSD}, phenylcyclidine, mushrooms, datura), volatile substances (gasoline sniffing, airplane glue, nitrites), marijuana (hashish), cocaine, alcohol, smoking, anabolic steroids, etc.

Among the factors contributing to drug abuse include burning the midnight oil at time of examination, sleeplessness, enhancing concentration, to get out of a difficult and tense situation, just for heck enhancing competence in athletics, etc.



Fig. 7.4: Substance abuse. Even in India and other resource-limited countries, adolescents are falling prey to the menace of substance abuse in a big way.



Fig. 7.5: Juvenile delinquency. Indulgence in unlawful activities, including violence on account of poor channelization of energies, is not uncommon in adolescents.

The most important preventive measure is channelization of the energy of the adolescents and creating awareness in them about the adverse effects of substance abuse. At times, services of a de-addiction center may be needed.

Pediatricians' role in substance abuse prevention lies in providing anticipatory guidance and counseling. Prevention and early intervention are quite cost-effective solutions to the menace. Even casual use of alcohol, tobacco and illicit drugs by adolescents—no matter how small or infrequent is accompanied by adverse health consequences and comorbidities. Also, See Chapter 6 (Developmental, Behavioral and Psychiatric Disorders).

Juvenile Delinquency

A proportion of adolescents repeatedly indulges in anti-social behavior in the form of pre-mediated planned and purposely unlawful activities (Fig. 7.5). Such adolescents usually come from emotionally disturbed or broken families residing in overcrowded unhealthy environments with poor amenities. Often, a basically timid adolescent may act out to demonstrate his adventurous spirit in the eyes of his peers and indulge in a delinquent act (gang psychology).

Prevention lies in improving the environmental and family settings. The pediatrician can play a pivotal role by interacting with parents, community leaders, social workers, school teachers and psychologist/psychiatrists and thereby provide a team approach to have the delinquent adolescent adjusted in the society.

In India, until recently, juvenile delinquents could be tried only by juvenile courts. Now, those with serious offences can be tried in the same way as adults. Also, See Chapter 6 (Developmental, Behavioral and Psychiatric Disorders).

Adolescent Violence and Aggression

The adolescent is especially prone to be assaulted physically or sexually. He is also vulnerable to develop behavioral problems, resulting in rejection by the parents, peer groups and school teachers. Some of them may indulge in violent crimes, including murders.

Adolescents with violent or aggressive behavior need evaluation for conduct disorders and attention deficit hyperactivity disorder (ADHD).

Management revolves around:

- **Psychosocial interventions:** Targeting underlying conduct disorder or ADHD, development of new skills and coping mechanisms, multisystem therapy, cognitive behavior techniques (CBTs), etc.
- **Psychopharmacological interventions:** Antipsychotics, antidepressants, stimulants, mood stabilizers, anxiolytics, beta-blockers, alpha agonists and even anti-epileptics. Lithium and sodium valproate are effective in such explosive disorders, conducts disorders and comorbid bipolar disorder. Adverse drug reaction (ADRs) such as enuresis, ataxia and weight gain limit use of lithium to a considerable extent.

Teenage Pregnancy

In India and most other developing countries, high incidence of teenage pregnancy is because of early marriage (on an average 16 years).

Of course, with increasing permissiveness and, consequent upon that, higher incidences of premarital sexual encounters, increasing number of pregnancies in unwed adolescent girls are occurring (Fig. 7.6).

- These pregnant adolescents are decidedly at increased risk for obstetric and perinatal complications such as toxemia, postpartum hemorrhage (PPH), postpartum infection, stillborn infants and LBW infants.
- Later, they have difficulty in proper care of the child and have a tendency to have multiple pregnancies and children.
- Those of the pregnant unwed girls who opt for abortion (usually at the hands of the unscrupulous quacks) too are at a special risk.

The pediatrician should put efforts for primary prevention of adolescent pregnancy. A sexually-active adolescent needs appropriate contraceptive advice. Introduction of sex education in schools may well help in safeguarding against early marriage, premarital sex and adolescent pregnancy.



Fig. 7.6: Teenage pregnancy. Pregnancy in adolescent girls is on the increase in spite of the fact that it is associated with several enhanced risks.

Sexually Transmitted Diseases and HIV/AIDS

Adolescents are on record as having an incredibly high incidence of STD (gonorrhea, syphilis, *Chlamydia*, chancroid, herpes genitalis, *Trichomonas*) and HIV/AIDS because of sexual experimentation (usually unprotected/unsafe sex), biological characteristics of the vaginal epithelium, and intravenous drug abuse.

Manifestations may be in the form of pathological vaginal discharge (leucorrhea) because of development of vulvovaginitis or cervicitis. Such symptoms as lower abdominal pain, vaginal discharge, pyrexia and irregular vaginal bleed point to the so-called PID.

STD and allied infections are a potential risk to the sexual partner as well and may later be responsible for such serious sequel as infertility and ectopic pregnancy.

The pediatricians must take the responsibility for creating awareness among adolescents about transmission and prevention of these infections. They should also have the high-risk adolescents identified through screening to enable them to have timely treatment.

Menstrual Problems

- **Amenorrhea:** Absence of menstruation may be primary or secondary. In **primary amenorrhea**, menarche has never occurred. In **secondary amenorrhea**, there is cessation of menses for more than three months after the establishment of a regular cycling. Table 7.5 lists the causes of amenorrhea in adolescent girls. Determination of etiology of amenorrhea in the adolescent girl should permit initiation of appropriate treatment in a good proportion of the cases.
- **Menometrorrhagia:** Excessive menstrual bleeding may be the result of dysfunctional uterine bleeding, congenital coagulopathies (von Willebrand disease), aspirin ingestion, thrombocytopenia, exogenous hormones (oral contraceptives), thyroid disorders, diabetes mellitus, estrogen-secreting ovarian tumors, trauma, infec-

Table 7.5: Important causes of amenorrhea in adolescent girls

Primary amenorrhea

- Chromosomal abnormalities
- Gonadal dysgenesis
- Triple X syndrome
- Isochromosomal abnormalities
- Testicular feminization
- Structural abnormalities
- Imperforate hymen
- Hematocolpos
- Hematometrium
- Agenesis of cervix or uterus.

Secondary amenorrhea

- Chronic illnesses
- Malnutrition
- Diabetes mellitus
- Inflammatory bowel disease
- Anorexia nervosa
- Cystic fibrosis
- Cyanotic congenital heart disease.

124 tion, pregnancy, or abortion. A gynecological consultation is in order.

- **Dysmenorrhea:** Painful menstrual cramps are a leading cause of short-term school absenteeism in adolescent girls. The dominant type is primary. **Secondary dysmenorrhea** is the result of a structural abnormality of the uterus or cervix, a foreign body, endometritis or endometriosis. In **primary dysmenorrhea**, use of a prostaglandin-synthetase inhibitor is of value.
- **Premenstrual syndrome (PMS):** It is characterized by manifestations such as breast engorgement and tenderness, fatigue, bloating, headache, increased appetite with craving for sweets and salty foodstuffs, weight gain, constipation, peripheral edema, irritability, mood swings, mental tension, and lack of concentration occurring 7–10 days before onset of periods and disappearing a day or two after the beginning of periods. The lifeline of management is reassurance.

BREAST DISORDERS/PROBLEMS

Breast Asymmetry

True asymmetry usually follows surgery, injury or infection. Pseudoasymmetry is, as a rule, associated with deformity of spine (scoliosis) or thoracic cage.

Breast Hypoplasia

Its causes include quite frail but tall girls, hypothyroidism, ovarian dysfunction (Turner syndrome), adrenal hyperplasia, and androgen-producing tumors. A surgical correction (mammoplasty) is possible.

Congenital Anomalies

These include supernumerary nipples (polythelia), absence of nipples (athelia), absence of breast (amastia) and inverted nipples.

Breast Mass

A breast mass in an adolescent is usually a cyst, a fibroadenoma or an abscess. Whereas cystosarcoma (a low-grade malignancy) is infrequent, carcinoma of breast is extremely rare during adolescence. In case of a mass that shows persistence or increase in size, an aspiration or excision biopsy is indicated.

Gynecomastia

Occurring in one-third of adolescent boys in early puberty, palpable development of breasts due to hormonal imbalance may be a matter of considerable concern (Fig. 7.7). It is transient and resolves within two years. Rarely, it may be large and persistent, warranting plastic surgery.

Nipple Discharge

In addition to pregnancy, galactorrhea in adolescents may occur as a result of local stimulation, drugs (oral contraceptives, antihypertensives, tranquilizers, heroin, codeine, marijuana, and amphetamines), pituitary or breast tumor or infection. Organic nipple discharge is termed as

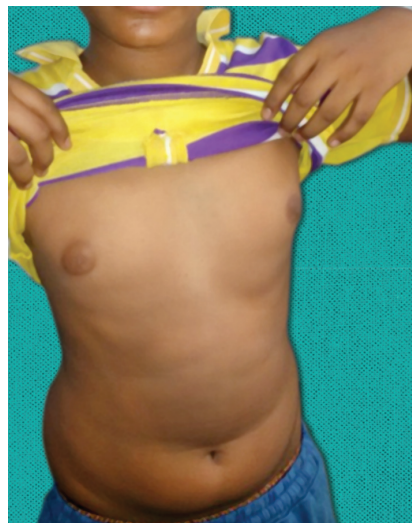


Fig. 7.7: Gynecomastia. Note the visible and palpable development of breasts in this 15-year-old. Though the matter of concern for the parents and the child, it resolves of its own in a matter of a year or two.

amenorrhea-galactorrhea syndrome in which serum prolactin level is raised.

Breast cancer is rare in adolescence. Persistence of a mass or its enlargement is an indication for aspiration and/or excisional biopsy.

PENILE PROBLEMS

Congenital Anomalies

These include hypospadias, epispadias, abnormal curvature, hypoplasia and erectile or ejaculatory dysfunction. If not attended to, the adolescent may suffer psychologically.

Skin Lesions

These include venereal warts (condylomata acuminata), which may even involve the urethra causing bleeding during voiding, genital herpes simplex causing edematous wheel and severe pruritus, syphilitic chancre over glans and prepuce, and chancroid with ulcer edges that are not indurated.

Balanitis and Balanoposthitis

Sepsis of the glans (balanitis) or foreskin (balanoposthitis) is a common problem and is nearly always associated with phimosis. In addition to local and oral antibiotic therapy, it is often advisable to carry circumcision for severe phimosis.

SCROTAL PROBLEMS

Undescended Testes

Cryptorchidism may be true or just a reflection of retractile testes, ectopic testes or absent testes. Delay in treating the condition may be complicated by testicular malignancy or infertility.

Hydrocele

When present, it is invariably of communicating type with the hernial sac.

UROLOGIC PROBLEMS

A majority of the urologic problems, including enuresis, in adolescents pertain to voiding dysfunction and are often psychosomatic in origin. Nevertheless, organic conditions such as urethral valves or strictures, spina bifida occulta, and infection should be considered in the differential diagnosis.

In case of urethritis (usually a manifestation of STD), leading symptom is dysuria with or without discharge that may be clear or purulent.

DERMATOLOGICAL PROBLEMS

Acne

It is the most common manifestation of increased level of androgens by increased size and secretions of sebaceous follicles and apocrine glands during adolescence. Over 80% teenagers suffer from it (Fig. 7.8).

It may be mild that clears in due course to severe that causes disfigurement of the face.

Since appearance is a matter of considerable concern to the adolescent, he needs to be offered proper guidance and, if the need be, treatment. He must wash face frequently, avoid cosmetics and squeezing the lesions. In case of girls, it must be ensured that pregnancy is not there before resorting to medication with tetracyclines and/or cisretinoic acid (isotretinoin).

Hirsutism

As a result of excess of androgens, an adolescent girl may develop an excessive male type growth of hair. Though the most common type is idiopathic, gonadal, adrenal, exogenous (drugs like androgenic steroids, minoxidil, diphenylhydantoin, cyclosporin, anabolic steroids, penicillamine, oral contraceptives, acetazolamide, diazoxide, danazol) and congenital anomalies (trisomy 18, de Lange syndrome) must be considered in differential diagnosis. Cosmetic correction is advisable. Simultaneously, attention should be directed to counter excessive androgens.

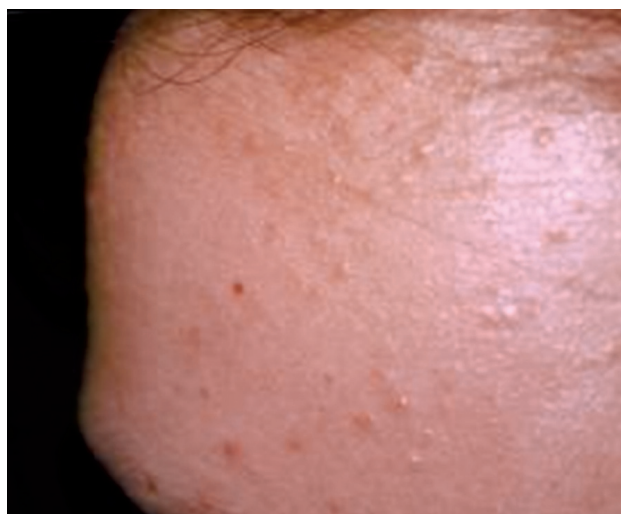


Fig. 7.8: Acne vulgaris. It occurs in a large majority of the adolescents, causing considerable concern to them.

Others

An adolescent's skin is vulnerable to other adverse influences like STD, HIV/AIDS, neurosis/psychosis (trichotillomania), contact sports (herpes simplex) and substance abuse.

SLEEP DISORDERS

Narcolepsy

It manifests as shortened rapid eye movement (REM) during wakefulness (sleep) with excessive day-time sleepiness, hallucinations, sudden flaccidity or even paralysis of a muscle group during sleep (cataplexy), and enhanced day-time sleepiness after disturbed night-time sleep because of apneic spells from airway obstruction (apnea-hypersomnia syndrome).

Insomnia

Adolescents are particularly prone to delayed bed-time (delayed sleep phase syndrome). This along with depression may contribute to insomnia in around 15 percent of the adolescents.

ORTHOPEDIC PROBLEMS

Problems such as slipped capital femoral epiphysis, idiopathic scoliosis, Osgood-Schlatter disease, costochondritis of the sternoclavicular joint (Tietze syndrome) on account of rapid growth of long bones, open epiphyses, increased traction at insertion of muscles and pulls and pressures of sports are common during adolescence.

Further, incidence of arthralgia from rubella, infectious mononucleosis and other viral infections is relatively high in adolescents.

Though infections of bones and joints are relatively less frequent in adolescents, these may follow as a complication of sickle-cell anemia or disseminated gonococemia.

About 10–14% adolescent girls and 5% boys manifest a slight curvature of the spine (scoliosis) during the peak of the height velocity curve. This requires no orthopedic attention unless the curve exceeds 10 degrees.

PROMOTION OF ADOLESCENT HEALTH

Health Education

Healthcare providers role does not end up with just health education. They must coordinate with other agencies to educate the adolescents on several related matters such as nutrition, sexuality and substance abuse etc. All efforts must be made to reach out to the adolescents, both schoolgoers and non-schoolgoers. For this objective, adolescent-friendly health services (AFHS) are needed. Use of mass media and school curriculum may also be made. Special stress should be on matters listed in Box 7.2. Improved knowledge about health matters and negative consequences of risk-taking behavior should be considered as an important step though not a foolproof, strategy for safe behavior among adolescents.

Box 7.2 Health education: Areas of special emphasis in adolescents

- Development of secondary sex characters
- Menarche, menstrual hygiene and associated problems in girls
- Seminal discharge in boys
- Body image
- Nutritional needs, including iron
- Managing emotions and stress
- Reproductive process, conception, childbirth
- Safe sex and contraception
- Right age for marriage
- HIV/AIDS, hepatitis B and other STDs
- Substance abuse, alcohol and tobacco.

Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; STD, sexual transmitted diseases.

Life Skills Education (LSE)/ Skills-based Education (SBE)

Life skills are abilities for adaptive and positive behavior so that the individual can deal effectively with demands and challenges of day-to-day life. SBE, given during face to face counseling, proves more effective in convincing the adolescent not to indulge in risk-taking activity such as violence, molestation and unprotected sex.

Family Life Education (FLE)

This WHO strategy is based on the observation that when adolescents are assisted to develop responsible attitudes towards relationship in the family settings, their emotional, psychological, social and sexual needs get satisfied. Its crux is awareness through education. Its various components include adolescent nutrition, personality development, understanding human sexuality and preparation for future parenthood.

Counseling for Managing Stress and Emotions

Stress is inability to cope with the demands. It causes **general adaptation syndrome**. It involves both nervous systems (predominantly autonomic), which reacts immediately and endocrine (hormone) system which takes time to react, but the reaction persists much longer. In fact, it affects almost all systems, including immune system, to certain extent.

Three types of stress are:

1. **Physical:** Overcrowding in class, bus; noise and environmental pollution.
2. **Psychological:** Intense academic demands.
3. **Psychosocial:** Conflicts with peers, teachers, family members.

The result of all these types is either estress or distress.

Estress promotes productivity and facilitates efforts. **Distress** causes loss of productivity and health problems. Adolescents need to be taught the art of stress management.

Nutritional Care and Counselling

A multi-sectoral approach should ensure sufficient food supply and its equitable distribution, and improved knowledge and information about nutrition, with special reference to healthy eating and healthy lifestyle and increased

needs during adolescence without any discrimination to the girl child. Nutritional promotion should operate at school, family (household) and community levels.

Immunization of the Adolescent

Adolescent immunization has remained a neglected area, exposing them to vaccine-preventable diseases. Just like adolescence that, until recently, was a no man's land! Neither the physician nor the pediatrician took proper care of the health problems of this key phase of life. Mercifully, adolescent immunization is now receiving attention in India as in other countries. Four goals of adolescent immunization are:

1. Catch-up vaccination for vaccines that had been somehow skipped during infancy and childhood.
2. Booster doses of such vaccines as tetanus toxoid, typhoid, pneumococcus.
3. Vaccine required to be given during adolescence and after.
4. Vaccination under special circumstances.

Tables 7.6. gives the IAP recommendations for catch-up immunization, Table 7.7 gives IAP recommendations in special circumstances and Table 7.8 represents latest IAP advisory committee on vaccines and immunization practices (ACVIP) immunization schedule for adolescents.

Table 7.6: IAP recommendations for catch-up immunization in adolescents

Vaccine	Schedule
MMR	2 doses at 4–8 weeks interval*
Hepatitis B	2 doses at 0, 1 and 6 months**
Hepatitis A	2 doses at 0 and 6 months (prior check for anti-HAV antibodies may be cost-effective)***
Typhoid	1 dose every 3 years****
Varicella	2 doses at 4–8 weeks interval

Abbreviations: MMR, measles, mumps and rubella; HAV, hepatitis A virus, IAP, Indian academy of pediatrics.

* One dose if previously vaccinated with one dose.

/ Combination of hepatitis B and hepatitis A may be useful in 0, 1, 6 schedule.

**** A minimum interval of three years should be observed between 2 doses of typhoid vaccine.

Table 7.7: IAP recommendations for adolescent immunization in special circumstances

Vaccine	Age recommended
Influenza vaccine	1 dose every year
JEV*	Catch-up, up to 15 years
PPSV23 (Pneumococcal) vaccine**	2 doses 5 years apart
Rabies vaccine O, 3, 7, 14, 28 day	As soon as possible after exposure

* Only in endemic areas as catch-up

** Maximum of doses two

Abbreviations: JEV, Japanese encephalitis vaccine; PPSV23, pneumococcal polysaccharide vaccine.

Table 7.8: IAP-Advisory Committee on Vaccines and Immunization Practices (ACVIP) recommended immunization schedule for adolescents

Vaccine	7–10 years	11–12 years	13–18 years
Tdap	1 dose (if indicated)	1 dose	1 dose (if indicated)
HPV*		3 doses	Complete 3— dose series
MMR	Complete	3—dose series	
Varicella	Complete	2—dose series	
Hepatitis B	Complete	3—dose series	
Hepatitis A	Complete	2—dose series	
Typhoid	1 dose	every 3 years	
Influenza vaccine	1 dose	every year	
JE vaccine	Catch-up	Upto 15 years	
Pneumococcal vaccine**			
Meningococcal vaccine***			

Abbreviations: HPV, human papilloma virus; MMR, measles, mumps and rubella; JE, Japanese encephalitis; Tdap, tetanus, diphtheria and acellular pertussis.

* HPV vaccines

Routine vaccination

- Minimum age—9 years
- HPV-4 (gardasil) and HPV-2 (cervarix) are licensed and available.
- Either HPV-4 (0, 2, 6 months) or HPV-2 (0, 1, 6) is recommended in a 3—dose series for females aged 11–12 years.
- HPV-4 can also be given to in a 3—dose series for males aged 11–12 years, but not yet licensed for use in males in India.
- The vaccine series can be started beginning at 9 years.
- Administer the second dose 1–2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).

Catch-up vaccination

- Administer the vaccine series to females (either HPV-2 or HPV-4) at age 13 through 45 years if not previously vaccinated.
- Use recommended routine dosing intervals (see above) for vaccine series catch-up.

** Pneumococcal vaccines

- Pneumococcal conjugate vaccine (PCV) and pneumococcal polysaccharide vaccine (PPSV) both are used in certain high-risk group of children.
- A single dose of PCV may be administered to children aged 6–18 years who have anatomic/functional asplenia, HIV infection or other immunocompromising condition, cochlear implant, or cerebrospinal fluid leak.
- Administer PPSV at least eight weeks after the last dose of PCV to children aged two years or older with certain underlying medical conditions, including cochlear implant.
- A single revaccination (with PPSV) should be administered after five years to children with anatomic/functional asplenia or an immunocompromising condition.

*** Meningococcal vaccines

- Recommended only in certain high-risk group of children, during outbreaks, and international travelers, including students going for study abroad and travelers to Hajj and Sub Saharan Africa.

contd...

contd...

- Both meningococcal conjugate vaccines (Quadrivalent MenACWY-D, Menactra by Sanofi Pasteur and monovalent group A, PsA-TT, MenAfriVac by Serum Institute of India) and polysaccharide vaccines (bi and quadrivalent) are licensed in India. PsA-TT is not freely available in market.

Early Diagnosis and Management of Medical and Behavioral Conditions

It is important to detect medical problems and behavioral problems (particularly unhealthy eating habits, substance abuse, sex-related problems, violence and aggression) early enough. Appropriate management in conducive environment and with assistance from pediatrician and, if the need be, from a psychologist/psychiatrist should in no case be delayed.

Legislation

Experience in Europe has demonstrated that legislation and regulatory policies discourage risk-taking behavior among adolescents. Nevertheless, there may be difficulties in implementation of such laws in a country like India. That restriction on smoking in public places, legislation against child labor and legal age of marriage—to name just a few—continue to be flouted mercilessly is well known.

INDIA'S LEAP FOR ADOLESCENT WELFARE: MISSION KISHORE UDAY

In 2013, the IAP launched a unique initiative, **Mission Kishore Uday**, to address the health needs of the adolescents in India. Approaches adopted in the initiative include interventions concerning counseling in such areas as:

- Normal body developments,
- Avoiding or minimizing the risk-taking behavior,
- Sexuality issues,
- Positive parenting, and
- Effective communication, etc.

The strategy has its roots in the conviction that parents have a major role in prevention of the health conditions in adolescents. It is the parents who have the sacred and honorable duty of rearing children with love and righteousness and by becoming role model and countering the negative messages from the media.

Through **Mission Kishore Uday**, IAP continuously encourages **3L** of positive parenting:

- **Love** for teenager,
- Set **Limits**, and
- Provide **Lattitude**.

Adolescents are the future of this nation and we as pediatricians have responsibility of shaping their future, by providing them the right kind of health and behavioral guidance.

Multiple Choice Questions

- The first sign of puberty in girls is:
 - Pubic hair
 - Breast bud
 - Menarche
 - Acne
- The first sign of puberty in boys is:
 - Pubic hair
 - Acne
 - Penis enlargement
 - Testicular enlargement
- Spot the wrong entry:
 - The IAP defines adolescence as the period of life between 10 and 18 years (inclusive)
 - Binge-eating adolescents are obsessed with persistent overconcern with body shape and weight
 - Ideally, puberty goiter should be treated with Lugol iodine
 - Gynecomastia in adolescent boys is transient, resolving in a couple of years without any pharmacotherapy
- Causes of hypoplasia of breasts in adolescent girls include each of the following, except:
 - Frail but tall girls
 - Hypothyroidism
 - XXX syndrome
 - Ovarian dysfunction (Turner syndrome)
- Most acceptable entry concerning adolescent immunization, except:
 - Catch-up vaccination for vaccines that had been somehow skipped during infancy and childhood
 - Booster doses of such vaccines as tetanus toxoid, typhoid, pneumococcus
 - Some vaccine are required to be specifically given during adolescence (say, HPV vaccine) and after
 - All of these.

Answers

1. B 2. D 3. C 4. C 5. D

Clinical Problem-solving

Review 1

A 15-year-old fairly built and fairly nourished healthy boy presents with deterioration in his scholastic performance and episodes of emotional lability over trifles during the past some 6 months. Examination shows acne and bilateral gynecomastia.

- Could his emotional symptoms and scholastic regression be related to acne and gynecomastia?
- How to handle this situation?
- What can be medically done for his acne?

Review 2

A 17-year-old college-going girl, suspected to be indulging in premarital sex, is a source of considerable anxiety for her parents.

- What are the risks involved in this sexually active teenager?
- What could be the role of the pediatrician in such a situation?
- What else can be done to safeguard against premarital sex and adolescent pregnancy on a large scale?

Answers

Review 1

- Yes, both could well be the cause of his scholastic regression and emotional symptoms.
- Apart from treatment of acne, this adolescent needs to be counseled in a conducive environment about the physiological basis of acne as well as bilateral breast enlargement. Once he is assured that these are just transient phenomena, his anxiety shall take a U-turn. If need be, assistance from a psychiatrist should be sought.
- He should be advised to wash face frequently, and avoid cosmetics and squeezing the lesions. Medication is in the form of antibiotics and local application of cis-retinoic acid (isotretinoin).

contd...

Review 2

1. There is every risk of her getting pregnant, placing her at risk of obstetrical and perinatal complications such as toxemias, postpartum hemorrhage, postpartum infection, stillborn baby and low birthweight baby. If abortion is opted for, this being usually conducted by unscrupulous quacks, places the teenager at a special risk.
2. Pediatrician's endeavor should be good counseling aimed at primary prevention of adolescent pregnancy. If avoidance of sexual activity is not workable, she needs an appropriate contraceptive advice.
3. Yes, introduction of sex educations in schools can assist in safeguarding against premarital sex and adolescent pregnancy.

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DEFINITION

By definition, biostatistics is the science of management of uncertainties in health and disease. It deals with the quantitative rather than the qualitative aspect of health and disease. The cornerstone of all biostatistical endeavors is the measurements through which all quantities are obtained and, thereafter, uncertainties and variations studied. This involves systematic collection, organization, analysis and interpretation of numerical data pertaining to health and disease. The measurements are employed:

- To assess the levels of health
- To assess the severity and level of disease
- To establish and interpret the reference values of various parameters
- To evaluate probabilities in diagnosis and management to assess the validity of medical tools.

The Apgar score, heart, respiratory rates, weight and height for age are the commonly used quantitative measurements for assessment of health and departure from it in case of infants and children. An example of assessing the severity of disease is the Glasgow scoring system that is employed to determine the level of unconsciousness.

The term, **medical statistics**, refers to statistics pertaining to medical sciences, data related to human diseases in particular. The term, **morbidity statistics**, refers to statistics pertaining to sickness. The statistics dealing with births, deaths and marriages fall under the category, **vital statistics**.

Important among the methods of presenting statistical data are:

- **Tables:** Tabulation is the first step towards employing data for analysis or interpretation.
- **Charts:** Bar charts (simple, multiple), histogram, pie chart, pictogram.
- **Diagrams**
 - Line diagrams—they tend to show trend of events with passage of time
 - Graphs
 - Pictures
 - Special curves.

A reasonable knowledge of the basics of biostatistics is essential for understanding data on health information. This, especially its pediatric component, needs to be considered an integral part of the health system.

THE CONCEPT OF NORMAL

The term **normal** denotes two potential meanings:

1. A person or process is healthy
2. Measured value falls within the normal range.

When we talk of normality in relation to growth and development, we indeed refer to quantitative normality. In terms of height, which is normally distributed within a population, a graph with the height on the X-axis and the number of children of that height on the Y-axis, a bell-shaped curve is formed. This curve indicates a **normal** or **Gaussian distribution**.

The peak of the curve corresponds to the arithmetical mean of the sample which, in turn, equals the median and the mode (definitions vide infra). **Skewed** is the term applied to a distribution in which the mean, median and mode are unequal. The limit within which there is clustering of the values in the vicinity of the mean determines the bell in the Gaussian distribution and is expressed mathematically by the term, **standard deviation** (SD), which is tied to the concept of normal distribution.

DATA, INFORMATION AND INTELLIGENCE

The terms are explained in Box 8.1. Remember that data that are not transformed into information and information that is not transformed into intelligence are of limited value only. These fail to guide the decision-makers, policy-makers, planners, administrators and health care personnel.

TYPES OF STUDIES

There are two major types of studies—cross-sectional study and longitudinal study.

1. **Cross-sectional study** refers to the study of a sample of individuals examined at one time only.
2. **Longitudinal study** refers to the study of a sample of individuals periodically at specific times. It is therefore, likely to take quite a long time but, nevertheless, is of greater relevance compared to cross-sectional study.

STATISTICAL AVERAGES

The term average implies a particular central value in the distribution around which the remaining values are distributed. It provides an idea about of the central value.

Box 8.1 Data, information and intelligence

- **Data** refers to discrete observations of attributes or events that need to be considered as a group collected from an institution or a system. Without various conversions, data are not of much statistical value.
- **Information** refers to the transformation of data by their reduction; summarization and adjustment for variations like the age composition of the population to enable comparisons over time and place are workable.
- **Intelligence** refers to the transformation of information through integration and processing with experience and perceptions based on social and political values.

Arithmetic Mean (Mean)

This is the most useful statistical average. It is calculated by adding the individual observations (summation) and then dividing it by the number of observations. It is denoted by the sign \bar{X} . If a measurement (X) of 10 adolescents is 20.5 cm, 21 cm, 20.2 cm, 19.8 cm, 21.5 cm, 20.3 cm, 19.7 cm, 20.5 cm, 21.1 cm, and 20.7 cm, the total becomes 205.3 cm. The mean is 205.3 cm divided by 10 which is 20.53 cm.

The Median

This is an average that does not depend upon the total and the number of items. The data is first arranged in an ascending or descending order of magnitude. Then, the value of the middle observation is the median. If the number of values is even, then the median is obtained by taking the average of the two middle values. Median is more representative of the average than the mean.

The Mode

This is the most commonly occurring value in a distribution of data. In the above mentioned example, since 20.5 is the most frequently occurring observation, the mode of the distribution is 20.5 cm. It is not often employed in pediatric statistics.

MEASURES OF VARIATION (DISPERSION)

The Range

This is the simple measure of dispersion. It is the difference between the highest and the lowest values in a given sample. Since it denotes only the extremes of two values and nothing in between, it is not of much value.

The Mean Deviation

This is the average of the deviations from the arithmetic mean and is given by the following formula:

$$\text{Mean deviation (MD)} = \frac{\sum (X - \bar{X})}{n}$$

The Standard Deviation

This is calculated as the root of the mean of the sum of squared deviation. The two formulas for the purpose are:

$$1. \text{ Standard deviation (SD)} = \sqrt{\frac{\sum (X - \bar{X})^2}{n}}$$

$$2. \text{ Standard deviation (SD)} = \sqrt{\frac{\sum (X - \bar{X})^2}{n - 1}}$$

where SD = standard deviation
S = sum of the squared deviation

First formula is basic and employed when sample size is more than 30. Second (i.e. modified) formula is for sample size less than 30.

The following steps are involved in calculating the standard deviation:

- Take the deviation of each value from the arithmetic mean.
- Now, square each deviation.

Table 8.1: Standard deviation: Interpretation in terms of observations falling within the range

Standard deviation (SD)	Percentage
One (plus/minus)	68.3
Two (plus/minus)	95.4
Three (plus/minus)	99.7

Table 8.2: Standard deviation: Probability of deviation from mean

Standard deviation (SD)	Percentage
One (plus/minus)	16.0
Two (plus/minus)	2.3
Three (plus/minus)	0.13

- Add up the squared deviations.
- Divide the result by the number of observations.
- Finally, take the square root. This gives the standard deviation. The prefix (+) to SD value indicates a dispersion to the higher side whereas the prefix (–) denotes the same to lower side.

One SD signifies that about 68% observations are within this range. Two SD signifies about 95% and three SD as high as 99.7% of the values lying within the particular range (Tables 8.1 and 8.2). In practice, it is infrequent to have values above two SD in a normal population.

Z Score

The term, Z score, is defined as the individual value in term of SDs above or below the normal (Gaussian) distribution curve. It assists in comparing observations between individuals. A child whose weight is less by more than 2SD below the mean is said to have minus Z (**–Z**) score. In case the weight is above the mean by 2SD, he is said to have positive (**+Z**) score.

Z score is helpful in comparing observations between individuals.

$$\text{Z score} = \frac{\text{observed value} - \text{mean value}}{\text{SD}}$$

Normal Distribution (Normal Curve)

This is a valuable concept in biostatistics. The limits on both sides of the mean are termed **confidence limits**.

- The area between one SD on both sides of the mean suggests about 68.3% values in the distribution.
- The area between two SD on both sides of the mean suggests about 95.4% values in the distribution.
- The area between three SD on both sides of the mean suggests 99.7 % values in the distribution (Fig. 8.1).

SAMPLING

For the sake of ease, economy and feasibility, a carefully obtained sample out of a large population of individuals, items or units is employed. The sample must be representative of the whole population. Three types of sample are:

1. Simple random sample
2. Systematic random sample
3. Stratified random sample

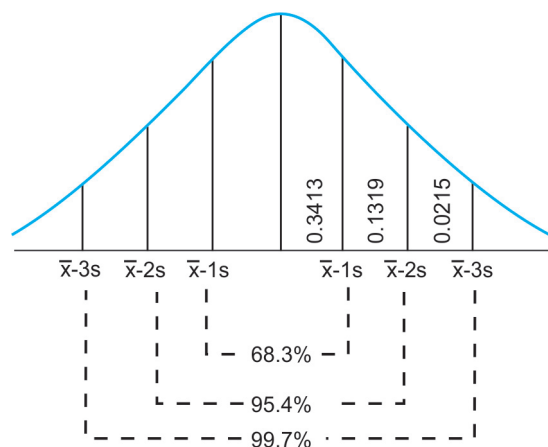


Fig. 8.1: Normal distribution curve.

In a sampling survey, three types of errors may occur:

1. Sampling errors
2. Non-sampling errors
3. Standard errors
 - Standard error of the mean
 - Standard error of the proportion
 - Standard error of the difference between two means
 - Standard error of difference between two proportions.

CHI-SQUARE TEST

Alternatively, the significance of difference between two proportions can be tested by the so-called **Chi-square test**. Chi-square test involves three steps:

1. Null hypothesis
2. Degree of freedom
3. Probability tables.

PERCENTILE

The term percentile refers to the frequency distribution curves. To be precise, the percentile is the percentage of an individuals in the group that have attained a certain measured quantity (say a weight of 17 kg or a height of 95 cm) or a developmental milestone. The percentile cutoffs may be calculated from the mean and SD. For example, the 5th percentile corresponds to -1.65 SD, 10th percentile to -1.3 SD and 25th percentile to -0.7 SD. Third percentile means that 97% cases are above and 2% below. Similarly, 20th percentile means that 80% cases are above and only 19% below. Generally, normal range of observations falls between 3rd and 97th percentile.

SIGNIFICANT (P) VALUE (Probability)

Consequent upon the appropriate analysis of data, a conclusion is required to be drawn whether the event being investigated had a certain probability of being secondary to a chance. The probability may well be very marginal in which case it is concluded that the event was not the result of a sheer chance.

Probability is referred to as the **p value**. When the value is equal to or less than 0.05, the study results are considered to be statistically significant. This means that there is only 1

Table 8.3: Interpretation of commonly employed expression pertaining to probability (p value)

p value	Significance (interpretation)
<0.001	Highly significant
<0.01	Very significant
<0.05	Significant
>0.05	Insignificant

in 20 chance or even less that the observed results occurred due to chance. The important expressions with significance are listed in Table 8.3.

ROLE OF STATISTICS IN GROWTH AND DEVELOPMENT

Statistically, the term, **normal**, denotes a set of values that generate a normal distribution curve, the so-called **bell-shaped Gaussian curve**.

In case of anthropometric data in growth and development, the peak of the bell corresponds to the arithmetic mean, median and mode of the sample. The extent to which the observed cluster nears the mean determines the width of the bell. It can be described mathematically by the SD. A measurement falling outside the normal range (say 2 SD or 3 SD) on either side of the mean should be regarded atypical.

A normal child is, therefore, defined as one whose characteristics fall within the range of measurements accepted as normal for majority of children in the same age group.

Percentiles constitute another way of relating an individual to a group. It indicates the percentage of individuals in the group achieving a certain measured quantity or developmental milestone. Percentile cutoffs may be calculated from the mean and SD.

Relationship between percentile lines on the growth curve and frequency distribution of height at different ages is shown in Figure 8.2. Method of percentile for developmental milestones is given in Figure 8.3.

Conventionally, observations between 3rd and 97th percentile curves or mean $+2$ SD are considered within normal range.

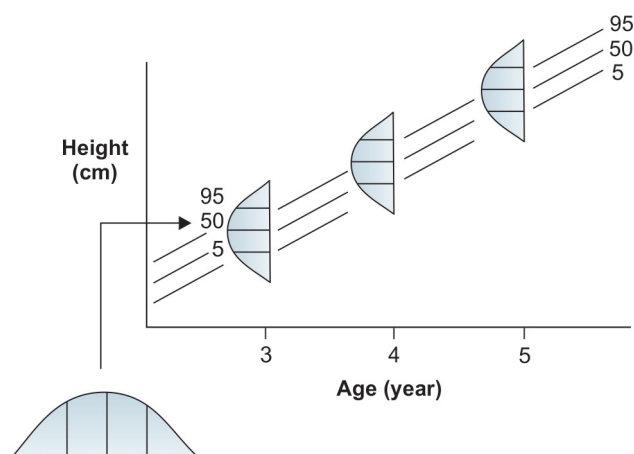


Fig. 8.2: Relationship between percentile lines on the growth curve and frequency distribution of height at different ages.

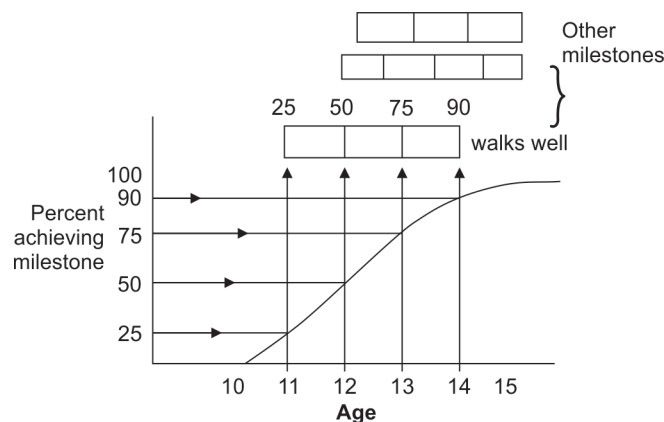


Fig. 8.3: Presentation of percentiles for developmental milestones.

Multiple Choice Questions

- What is the most appropriate entry about aims and objectives of applications of biostatistics?
 - To assess the levels of health and the severity and level of disease
 - To establish and interpret the reference values of various parameters
 - To evaluate probabilities in diagnosis and management and the validity of medical tools
 - All of the above
- Spot the wrong observation about the "normal":
 - "Normal" denotes that a person or process is healthy, and measured value falls within the normal range
 - Gaussian distribution is a bell-shaped curve
 - Skewed is the term applied to a distribution in which the mean, median and mode are equal
 - Standard deviation is tied to the concept of normal distribution
- Each of the following entries are correct, except:
 - 3 SD means 99.7% chance of the values falling in the said range and only 0.3% probability of deviation from mean
 - Z score is same as SD and helps in comparing values between individuals
 - Third percentile means that 97% cases are above and 2% below
 - Probability (p) value >0.5 is insignificant
- True observation include all except:
 - Observations between 3rd and 97th percentile curves or mean + 2 SD are considered within normal range
 - Percentile cutoffs may be calculated from the mean and SD
 - Percentile concept cannot be applied to developmental milestones
 - A child with a weight <3rd percentile is considered is considered suffering from "failure to thrive"
- Which of the following is a correct entry?
 - It deals with the qualitative aspect of health and disease
 - Charts such as bar charts (simple, multiple), histogram, pie chart, pictogram are the first step for applying data for analysis and interpretation
 - The limits on one sides of the mean are termed confidence limits
 - Since range denotes only the extremes of two values and nothing in between, it is not of much value

Answers

1. D 2. C 3. B 4. C 5. D

Clinical Problem-solving

Review 1

A 6-year-old weighs 14 kg against the standard weight of 20 kg at 6 years. This weight falls below 2 SD of the mean.

- Roughly, what is his Z score?
- How is the exact Z score calculated?
- What is special value of Z score?

contd...

Review 2

A 5-year-old child presents with stunting despite good weight. His height of 85 cm turns out to be falling <3rd percentile.

1. How do you interpret the observation "<3rd percentile"?
2. How will you define percentile?
3. How are percentile cutoffs calculated?

Answers**Review 1**

1. Since this child's weight is less by more than 2 SD of the mean, his Z score is minus Z (–Z).
2. The formula for exact Z score is as follows:

$$Z \text{ score} = \frac{\text{observed value} - \text{mean value}}{\text{SD}} = \frac{14 - 20}{2} = \frac{-6}{2} = -3 Z$$

3. Z score assists in comparing observations between individuals.

Review 2

1. The observation of the child's height falling <3rd percentile means that 97% children of his age are above and only 2% below his height. This signifies a severe stunting.
2. The percentile is the percentage of an individuals in the group that have attained a certain measured quantity (say a weight of 17 kg or a height of 95 cm) or a developmental milestone.
3. The percentile cutoffs may be calculated from the mean and SD. For example, the 5th percentile corresponds to –1.65 SD, 10th percentile to –1.3 SD and 25th percentile to –0.7 SD.

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HEALTH BY PEOPLE

Health is no longer conceived as an *absence of disease*. The World Health Organization (WHO) definition of health, which is now universally adopted, is as follows:

Health is a state of complete physical, mental and social wellbeing, and not merely an absence of disease or infirmity.

An individual living in a state of physical, mental and social wellbeing is said to be enjoying positive health which is a basic human right and a worldwide social goal. The importance accorded by the WHO to health is reflected in its laudable resolve of ***attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a social and economically productive life.*** This is a different matter that the goal could not be fully met by the set deadline.

The concept of ***Primary health care*** dates back to Alma Ata Declaration of 1978. According to this WHO approach, based on principles of social equality, nation-wide coverage self-reliance, intersectoral coordination and people's involvement, ***rural population of developing countries must have a provision of at least the base minimum of health services.*** The approach has been described as:

Health by the people,

Placing people's health in people's hands.

This concept is eminently most applicable to child population, more so in the resource-limited world.

COMMUNITY PEDIATRICS

DEFINITION

The term, community pediatrics, denotes a synthesis of clinical practice and public health principles directed toward providing health care to a given child and promoting the health of all children within the context of the family, school, and the community by using community's resources in collaboration with other professionals, agencies, and parents.

The aim is to achieve optimal accessibility, appropriateness, and quality of services for all children, and to advocate especially for those who lack access to care because of social or economic conditions or their special health care needs in the community setting.

COMMUNITY PEDIATRICS AS A COMMITMENT

Community pediatrics is one of the first clinical disciplines to connect with community medicine with a huge compo-

nent of preventive and social medicine. It should be considered a concept rather than a branch of pediatrics, implying that ***health is determined by interaction between the child, his environment and the society in which he lives.*** It is, by no means, a measurable quantity, independent of this vital relationship.

In other words, community pediatrics means pediatrics as it applies to the child, his family and the community. The child care covers health and disease from conception to adolescence. The objective is to carry the health care to the doorstep of the needy through various categories of workers, including those trained at grass-root level. In the resource-limited countries, great majority of the vulnerable population lives in villages, periurban slums and labor colonies. The most practical approach is to carry out the health care within the home environment or in the neighborhood of the family.

Yet, it is wrong to think that the term refers to the practice of pediatrics only outside the hospitals. Undoubtedly, the latter are a part and parcel of the community. As a matter of fact, hospitals are important component of the community as health centers, schools, crèches, and homes for the handicapped or the daycare centers.

BASIC PRINCIPLES

Two essential areas of study in community pediatrics are:

1. Health of child population in relation to its social environment, i.e. the total community.
2. Health of the individual child as a result of multitude of social influences (both positive and negative).

Whereas the first constitutes a part of social medicine, the second is a part of clinical medicine. Both have got to operate together for the rational delivery of preventive and curative services to the vulnerable population.

No doubt, the principles of community pediatrics remain more or less the same in developing as also the developed countries. Their application, of course, varies from country to country. This is important, also in view of the fact that each country may have its special problems needing priority attention. In the same country, there may also be regional variations—in fact variations from community to community.

ADVANTAGES

Advantages of community pediatric are multipronged (Box 9.1).

Box 9.1 Advantages of community pediatrics

- Health care goes to the susceptible child population, thus ensuring protection to those who may not otherwise seek advice.
- The concept ensures community participation at all stages.
- A community based pediatric project can be started in a simple mud-walled/tiled structure. The equipment and manpower are locally available at relatively low cost.
- It monitors the health and nutritional status of infants and children on a continuing basis. This considerably brings down morbidity and mortality.
- It contributes enormously to family welfare by ensuring survival of the child and convincing the parents of the advisability, to restrict the number of children to 1 or 2.
- It reduces undue burden on the hospitals which, in any case, are not the right place for tackling most of the problems encountered in the developing regions.

Box 9.2 Types of prevention

- **Primary prevention:** Preventing occurrence of a disorder per se.
Examples: Immunization, portable drinking water, proper sewage disposal.
- **Secondary prevention:** Identifying and eliminating precursor of a disease.
Examples: Screening for thyroid disorders, blindness; long-acting penicillin (benzathine penicillin) prophylaxis in rheumatic fever.
- **Tertiary prevention:** Halting development of disabilities from an established disease.
Examples: Physiotherapy in poliomyelitis or cerebral palsy.

PREVENTIVE PEDIATRICS

The term, pediatrics, refers to child health care from conception to adolescence. By the term, **preventive pediatrics** is meant *prevention of disease and promotion of physical, mental and social wellbeing of children with the aim of attaining a positive health*. Pediatrics, in actuality is largely preventive in its objective.

It is broadly divided into two:

1. **Antenatal preventive pediatrics** includes measures such as adequate nutrition of the pregnant mother, prevention of communicable diseases, preparation and education of the mother for delivery, mothercraft and breastfeeding, etc.
2. **Postnatal preventive pediatrics** includes measures such as periodic medical checkup of infants, supervision of nutrition, immunization, accident prevention, and psychological supervision.

Prevention in pediatrics may be—primary, secondary or tertiary as represented in Box 9.2.

SOCIAL PEDIATRICS

By the term, **social pediatrics** is meant *application of the principles of social medicine to pediatrics in order to obtain a more complete understanding of the problems of children so as to prevent and treat disease and promote their adequate growth and development through an organized health structure*.

Social pediatrics, therefore, is understandably concerned with the delivery of comprehensive and continuing

Box 9.3 Major health needs of the child

- Healthy and happy parents
- Balanced and nutritious diet
- Clean, healthful house and living environments
- Developmental needs such as play, amusement; love, affection, security; recognition; recreation; company of other children
- Educational provisions/opportunities.

child health care services and to bring them within the reach of the total community.

In order to ensure adequate physical, mental and social growth of the child, we must meet his total health needs (Box 9.3).

The coordination between social pediatrics, social obstetrics and social medicine has made a sea change in providing comprehensive mother and child health (MCH) care services, including family welfare/planning. Nothing short of this strategy is likely to promote community health, especially in the developing world.

ANTICIPATORY PEDIATRICS

The term, **anticipatory pediatrics** implies anticipation of certain happenings in the growth and development of the child, both normal and abnormal, including disease. As a result, the parents remain prepared for certain developments and the attending doctor can plan preventive measures for the untoward developments.

In case of a disease, he can anticipate the complications/sequela and take preventive action, or, if that is not workable, take early action for treatment.

TOTAL PEDIATRIC CARE

The term, **total pediatric care** denotes preventive, promotive, educative, curative and rehabilitative services to the child. In nutshell, it covers all facets of child care and welfare—the **total (whole) child**, so to say.

FAMILY HEALTH

Family health refers to the overall health of the individual family members. It takes into account the interrelationship and interdependence of the physical and mental health states of individual family members who live together. Thus, it determines and at the same time is determined by the effective functioning of the family as a biological and cultural unit with a cultural setting.

FACTORS INFLUENCING FAMILY HEALTH

- **Environmental:** Housing and sanitary conditions, drinking water and environmental pollution.
- **Social:** Socioeconomic status, nutritional status, level of literacy, fertility rate and family size.

FAMILY HEALTH PROGRAM

In practice, family health has come to mean the sum-total of MCH, nutrition, health education, immunization and family planning. The successful operation of the strategy

can induce families to assume responsibility for their health and welfare. This is a contribution to the community either.

The essential criteria of a sound family health program are:

- It should be able to offer primary, preventive and promotive health care, as a continuous process rather than at intervals.
- The population should have these facilities at the doorstep.
- It should be backed by a sound referral unit, available at a short distance.

MATERNAL AND CHILD HEALTH SERVICES

The term, **maternal and child health (MCH)** denotes promotive, preventive, curative and rehabilitative health care for mothers and children, including maternal health, child health, family planning, school health, handicapped/disabled children, adolescence and health aspects of child care in special settings such as a day care center.

The concept highlights the vital importance of considering the mother and the child as a single unit (Fig. 9.1). The health of the child is by and large dependent on mother's health and attitudes. During care of the mother, attention to the child (both in utero and afterwards) is nearly always mandatory.

There is a growing feeling that the concept of mother and child as a single unit needs to be extended to include father since his role in both child's and mother's health and welfare remains significant (Fig. 9.2).

Objectives

Specific aims and objectives of MCH includes:

- Reduction in maternal, perinatal, infant and child mortality and morbidity.
- Promotion of reproductive health, e.g. postponing unwanted arrival of child, adequate spacing between two children and containment of population explosion.
- Promotion of physical and psychological development of the child as also the adolescent within the family.



Fig. 9.1: Mother and child should be considered as a single unit. Mother's health and attitudes have a considerable bearing on child's health, growth and development.



Fig. 9.2: Mother, child and father as a single unit. This is a projected concept—in a way, a further extension of the time-honored "mother and child as a single unit" concept.

Delivery

The overwhelming problems affecting the mother and the child in developing countries at present revolve around the triad of malnutrition, infection and the hazards associated with uncontrolled reproduction/fertility.

The problem of malnutrition may be tackled in two ways:

1. **Direct intervention** includes activities such as supplementary feeding programs, fortification of food, distribution of iron, folic acid, vitamin tablets, nutritional education, etc.
 2. **Indirect intervention** includes measures such as control of communicable diseases through immunization, improvement of environmental sanitation; provision of clean drinking water, food hygiene, production of more food, education and primary health care.
- Problem of infection in the mother as well as the child needs to be tackled by preventive measures such as:
- Immunization of the mother and the child,
 - Personal hygiene and appropriate sanitary measures, and
 - Education of the mother in medical measures like oral rehydration in diarrheal disease and febrile illnesses.

Recognizing the importance of tackling the triad of malnutrition, infection and uncontrolled reproduction/fertility, MCH services in India are now offered as a package to promote continuity of care and reduce number of visits the mother has to make for herself and for the child.

Box 9.4 and 9.5 list the important components of the MCH care package and mortality indicators employed for MCH care, respectively.

NATIONAL HEALTH MISSION

Since the year 2005, India has been aggressively promoting its flagship program, National Health Mission (NHM),

Box 9.4 Important components of the maternal and child health (MCH)

- Antenatal care
- Intranatal care
- Postnatal care
- Perinatal care
- Nutrition advice
- Immunization
- Primary health care
- Rational family planning.

Box 9.5 Mortality indicators employed for assessing the maternal and child health (MCH)

- Maternal mortality rate
- Infant mortality rate
- Neonatal mortality rate
- Post-neonatal mortality rate
- Perinatal mortality rate
- Under-fives mortality rate
- Child survival rate.



Fig. 9.3: National Health Mission: Currently, this is India's flagship program having under its umbrella several, health-centric schemes, initiatives and programs.

under which many schemes, initiatives and programs are brought to provide universal access to quality health care (Fig. 9.3). It is in operation in two major forms, namely—**National Rural Health Mission** (NRHM) and **National Urban Health Mission** (NUHM).

Since 2013, NRHM stands augmented with a new program, **Reproductive, Maternal, Newborn, Child and Adolescent Health (RMNCH + A) strategy**. The much-needed extra thrust on neonatal and adolescent health is the objective of this initiative. Salient features of the initiatives have already been described in Chapter 1 (Pediatrics: Contemporary Trends).

INTEGRATED CHILD DEVELOPMENT SERVICES (ICDS) SCHEME

This scheme was first introduced in 1975 on experimental basis in the form of 33 projects; has now over 5,000 projects. It is targeted at holistic development of children (Fig. 9.4).

Objectives

- To improve the nutritional and health status of children in the age group 0–6 years.
- To lay the foundation for proper psychological, physical and social development of the child.
- To reduce the incidence of mortality, morbidity, malnutrition and school dropout.
- To achieve effective coordination of policy and implementation amongst the various departments to promote child development.



Integrated child Development Services

Fig. 9.4: Integrated child development services scheme: Major objective is to promote child development with special reference to health and nutritional status.

- To enhance the capability of the mother to look after the normal health and nutritional needs of the child through nutrition and health education.

Package of Services

- Essential
 - Supplementary nutrition
 - Immunization
 - Health check-up
 - Referral services
 - Nutrition and health education
 - Nonformal education.
- Supplementary nutrition aims to provide
 - 500 kcal and 12–15 g protein per day to children between 6 months and 6 years;
 - 800 kcal and 20–25 g protein to severely malnourished children; and
 - 600 kcal and 18–20 g protein to pregnant and lactating mothers per day.
 - For children below 3 years food is given as take-home ration.

Beneficiaries of Services

The major beneficiaries of ICDS are children under 6 years of age and pregnant and lactating mothers. Besides, women in the age group 15–44 years are also included. Thus, beneficiaries constitute over 40% of the total population. The scheme is jointly operated by the Ministry of Health and Family Welfare and Ministry of Women and Child Develop-

Table 9.1: Services available to different categories of beneficiaries

Beneficiary	Services
Children under 1 year	<ul style="list-style-type: none"> • Supplementary nutrition • Immunization • Health check-up • Referral services
Children of 1–3 years age group	<ul style="list-style-type: none"> • Supplementary nutrition • Immunization • Health check-up • Referral services
Children of 3–6 years age group	<ul style="list-style-type: none"> • Supplementary nutrition • Immunization • Health check-up • Referral services
Expectant and nursing mothers	<ul style="list-style-type: none"> • Nonformal preschool education • Health check-up • Immunization against tetanus of expectant mothers • Supplementary nutrition • Nutrition and health education
Other women of 15–44 years age group	Nutrition and health education

ment. The services offered to different categories of beneficiaries are shown in the Table 9.1.

ICDS scheme ought to be viewed as a vital drive against poverty and as an instrument to improve the health, nutritional and educational status of the under privileged children and mothers as a part of India's 20-point development plan. What is remarkable is that, according to conservative estimates, it will cost less than even 1% of the gross domestic product of the country.

Delivery of Services

The services are delivered at a community center, the **anganwadi** (meaning a courtyard). Anganwadi worker (AWW) is the backbone of the center. She comes from a local community and has had four months of training in fundamentals of child development, nutrition, immunization, personal hygiene, environmental sanitation, antenatal care, breastfeeding, identification and immediate management of at-risk children, treatment of common day-to-day illnesses, preschool education and functional literacy and simple record keeping. In each urban ICDS project, AWW must at least be a matriculate, but that is not necessary for rural and tribal projects.

The AWW is assisted by a local person, usually an uneducated and unskilled woman.

The work of AWW is supervised by mukhyasevika. She is a graduate and has had two months special training.

The **Child Development Project Officer** (CDPO) supervises the work of mukhyasevikas and is in charge of each ICDS project. She/he is preferably a graduate in child development, social work, home science, nutrition or any allied field and has had two months special training.

The ICDS scheme is under the administrative control of the Social Welfare Ministry, Government of India. At the State level too, social welfare is under the administrative ministry in a vast majority of the States.

In rural projects, the services are strengthened by the primary health centers whereas in the urban ones, medical colleges make outstanding contributions. Training consultants (drawn from community medicine or pediatrics) provide services related to training, survey and research.

Community Participation

All attempts must be made to explain different components of the program to the community so that people feel involved in it. Community needs to be involved through local health committees in the preparation of nutritious food mix for supplementary nutrition, using local foods, immunization, vitamin A, iron and folic acid supplementation, etc. Mahila mandals can play valuable role in ICDS activities.

The major thrust of ICD scheme at present is to achieve a convergence between sectoral services of various departments involved in the upliftment of underprivileged sections of the community. AWW are expected to play a significant role in this endeavor.

CHILD LABOR

Child labor may be defined as employment of children in gainful occupations even at the expense of their physical, emotional and social wellbeing. Labor, for the purpose of this definition, should be interpreted as work that the child does outside his own family circle and for which he, in turn, receives wages. Work in this case as such requires strength or patience rather than skill or training.

MAGNITUDE OF THE PROBLEM

According to the International Labor Organization 2012 report, 168 million children around the world are engaged in child labor, accounting for 11% of the world's child population.

According to a conservative estimate, over 80 million children aged less than 15 years are engaged in child labor in the world. What is remarkable is that 98% of them are in the developing countries. The Anti-slavery society believes the number may well be much more than 100 million since in many countries child labor may be clandestine and children who both work and attend school are rarely considered as child workers.

India has the largest force of child laborers in the world, about 90% of them being in rural areas. Every third house has a working child. Every fourth child is employed. In India's national capital alone, 5,00,000 children are estimated to be working in shops or wayside eating places (dhabas), as domestic servants, or street children (rag-pickers, for instance).

MAJOR PATTERNS OF CHILD LABOR (FIGS 9.5A AND B, FIG. 9.6)

- **Unorganized sector:** A vast majority of the child labor force is in the unorganized sector—agriculture work, as shoeshine boys, rag-pickers, newspaper vendors, cigarette vendors, helpers in shops and small wayside restaurants or petty servants' for running errands in private homes.



Figs 9.5A and B: Child labor. (A) Two child laborers engaged in a strenuous manual work at a construction site; (B) An instance of street children who collect garbage the whole day and are banked upon by the family as bread-earners.



Fig. 9.6: Child labor. A glaring example of working children who rakes through garbage dumps for polythene bags, plastic and waste paper for a living.

- **Organized sector:** Only a small proportion of working children are in the real organized sector. In actuality, it is the semi-organized sector—carpet weaving, sari embroidery, brassware, precious stone polishing, *bidi* making, bangle manufacturing, leather tannery, match and firework manufacturing, construction work, gas stations, petrol pumps, automobile workshops and autogarages, etc. which monopolize the situation.

All said and done, remember that the largest number of working children is found in households, frequently helping adults in household chores or providing baby-sitting for the younger siblings. Next comes the nondomestic work—usually agricultural in nature. All sort of work under the eponym child labor nearly always discourages school attendance.

BACKGROUND FACTORS

- Poverty is the single most important factor responsible for child labor.
- Exploitation by the parents, who have selfish motives in wanting their children to work rather than go to school, is often the operative cause.
- Other factors include exploitation by the employers, bad company, begging gang, school dropout, child-out-of-wedlock, maladjustment in the family, death of parent(s) and juvenile delinquency.

HEALTH HAZARDS

- **Environmental hazards:** The working child is exposed to adverse factors such as dust, smoke, lighting, and radiation, unsafe and unhygienic conditions—to mention just a few—all of which threaten his health.
- **Drug abuse:** Child laborers are frequently exposed to smoking, boozing and drugs which eventually lead to addiction and far-reaching damage to child's health.
- **Venereal diseases:** Child prostitution and sexual exploitation may lead to venereal diseases (VD).
- **Occupations hazards/accidents and injuries:** Incidence of injuries while working is quite high. The leading causes include lifting of heavy weights, broken glasses, slipping or falling, and injuries caused by various materials and machinery.
- **Communicable diseases:** There is evidence that the working children have much higher incidence of communicable diseases such as tuberculosis, leprosy and VD.
- **Malnutrition:** Poor nutrient intake in relation to increased needs, more so as a result of increased manual work, adversely affects the normal growth spurt during puberty and adolescence. Child laborers are known to suffer from poorer growth and health status compared to their nonworking counterparts.
- **Psychosocial development:** Restricted social interaction with denial of leisure, play and recreation, and long hours of daily work leave crippling effect on child's emotional development. With exposure at a premature age to adult life of brawls, sex, boot-logging, crime and what not, he is thrown into life, incredibly precocious beyond his years.
- Little wonder, smoking, drug addiction, smuggling and even prostitution are common in working children. Juvenile delinquency is very high in such children.
- **High morbidity:** Magnitude of ailments, say headache, backache, cold, cough, fever, conjunctivitis, scabies, pyoderma, nutritional deficiency states, tuberculosis, intestinal parasitic infestations, diarrheal disease and accidents, etc. is far higher in child laborers. More than

Table 9.2: Health hazards in child labor

Type of labor	Health hazard(s)
Agriculture	<ul style="list-style-type: none"> Injuries from accidents Heat-induced problems Dermatitis from fertilizers, pesticides or herbicides, snake bite, etc Parasitic infections
Carpet-making	<ul style="list-style-type: none"> Lung problems from inhalation of fiber dust Poisoning from coloring agents
Balloon factory	<ul style="list-style-type: none"> Lung problems including pneumonia Heat failure
Bidi industry	<ul style="list-style-type: none"> Nicotine poisoning in the form of easy fatigability of muscles Nausea Headache Blackouts Blindness
Powerloom industry	<ul style="list-style-type: none"> Lung problems like byssinosis and tuberculosis
Firework/match industry	<ul style="list-style-type: none"> Lung problems Burns Muscle fatigability Deformities
Zari industry	<ul style="list-style-type: none"> Eye problems Spinal problems Deformities
Glass industry	<ul style="list-style-type: none"> Heat stroke Lung problems Conjunctivitis Reduction in life span
Look industry	<ul style="list-style-type: none"> Lung problems including—asthma Acid burns
Brass industry	<ul style="list-style-type: none"> Lung problems Acid burns
Slate industry	<ul style="list-style-type: none"> Silicosis Pneumoconiosis Tuberculosis
Domestic work	<ul style="list-style-type: none"> Fatigability CAN Drug abuse
Prostitution	<ul style="list-style-type: none"> VD AIDS Hepatitis

Abbreviations: CAN, child abuse and neglect; VD, venereal disease; AIDS, acquired immunodeficiency syndrome.

the work, the working conditions are harmful to the health.

Table 9.2 lists the health hazards in relation to type of labor.

THE WAY-OUT

- Child labor is closely connected with the socio-economic status of the deprived communities—say poverty, illiteracy and unemployment. Banning it, though eventually needed, is neither workable nor desirable at present in view of widespread poverty and bad economy.
- The thrust right now should be on elimination of child labor related to exploitative and hazardous works, and to bring health services where they work through a

Table 9.3: Main features of the Child Labor (Protection and Regulation Act 1986)

- No child who has completed his 12th year and no adolescent shall be required or allowed to work in any plantation unless:
 - A certificate of fitness granted with reference to him under section 27 is in the custody of the employer, and
 - Such child or adolescent carries with him, while he is at work, a token giving a reference to such certificate.
- No child shall be required or permitted to work in any establishment in excess of such number of hours as may be prescribed for establishment.
- The period of work on each day shall be fixed in a way that no period shall exceed three hours before he has had an interval for rest for at least one hour.
- The period of work should be so arranged that, inclusive his interval for rest under subsection two, it shall spread waiting for the work on any day.
- No child shall be permitted or required to work between 7 pm and 8 am.
- No child shall be required or permitted to work overtime, etc.

strategy involving the parents, employees, community, and non-governmental, governmental and voluntary agencies.

- These children need to be essentially protected against exploitation, abuse, maltreatment and health hazards.
- It is also important to regulate working conditions in areas in which they are lawfully permitted to work.
- The highlights of *The Child Labor (Prohibition and Regulation) Act, 1986*, in our country are listed in Table 9.3. Most glaring feature of the act is that, except the family-based work or recognized school-based activities, children are not expected to work in occupations concerned with agriculture, industry, etc.
- Disillusioned by the worsening child labor scenario in India, the Supreme Court of India in 1996 directed all State Governments and Union Territories to take concrete steps to abolish child labor. It identified nine industries for priority action and directed setting up of Child Labor Rehabilitation Welfare Fund. The offending employers are supposed to pay for each child a compensation of ₹ 20,000 to be deposited in the Fund.
- The Indian Academy of Pediatrics (IAP) Committee on Child Abuse, Neglect and Child Labor (CANCL) has formulated an ambitious countrywide strategy to fight the malady.

STREET CHILDREN

As many as 100 million children across the globe, with dominant concentration in Asian, African and Latin American countries, live and work on streets, usually without support from families.

Major factors contributing to this malady are poverty, rapid urbanization, loss of family members through disease, accidents or disasters, physical and sexual abuse, etc.

Street children (Fig. 9.7) are especially at risk of developing nutritional deficiencies, tuberculosis, sexually transmitted disease (STDs), human immunodeficiency virus (HIV), substance abuse, skin disorders, intestinal parasitosis, prostitution and criminal exploitation.



Fig. 9.7: Street children. Poverty, rapid urbanization, loss of family members through disease, accidents or disasters, physical and sexual abuse figure among the multitude of causes.

The governmental and non-governmental organizations (NGOs) need to intensify efforts to improve their lot through:

- Provision of health and welfare services
- Housing opportunities
- Educational facilities
- Employment
- Adoption
- Rehabilitation centers.

CHILD TRAFFICKING

According to United Nations Children's Emergency Fund (UNICEF), child trafficking is defined as movement of children less than 18 years from their native places to different places in or even outside the country for clandestine and exploitative purposes in activities such as prostitution, cheap labor, begging, bondage, slavery, militancy, etc. Children are taken away from their families, communities and support network. They are left isolated and vulnerable to exploitation. According to conservative estimates, over a million children every year get involved in trafficking.

Government of India (GoI) has launched **Ujjawala**, a comprehensive scheme aimed at creating protective environment for children. Its 5 components are:

1. Prevention
2. Rescue
3. Rehabilitation
4. Reintegration
5. Repatriation.

THE HANDICAPPED CHILD

The term, **handicap**, refers to an inability to achieve the full potential or fulfill a role that is normal for that individual as a result of disease, impairment or disability. It is the effect of the conditions, e.g. inability to participate in competitive sports like hockey, cricket or skating in post-polio lameness, or social isolation resulting from mental retardation, deafmutism or epilepsy.



Fig. 9.8: Handicapped child.

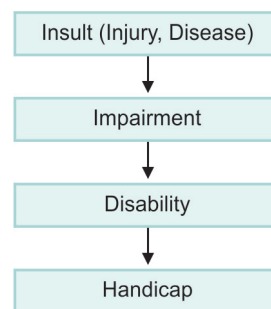


Fig. 9.9: Sequence of events leading to a handicap.

Disease, on the other hand, simply refers to a specific health problem like cleft palate, arthritis or congenital heart disease.

Impairment refers to any loss or abnormality of psychological, physiological or anatomical structure or function like autism, impaired vision or loss of a limb in an accident.

Disability refers to an inability to carry out certain activities considered normal for the individual's age, sex, etc. as a result of impairment.

According to a conservative estimate, 10% of India's population is handicapped in one way or the other. Thus, there are about 45 million handicapped children in the country at present. Worldwide, there are about 400 million handicapped children (Fig. 9.8). Figure 9.9 gives the sequence of events leading to a handicap.

ETIOLOGIC CLASSIFICATION

Communicable diseases, perinatal insult, protein energy malnutrition (PEM) and accidents together account for 75% of the handicap in childhood. Table 9.4 presents the detailed etiologic classification of pediatric handicap.

REHABILITATION

Rehabilitation of the handicapped aims at training and retraining of the individual to the highest possible level of functional ability through combined and coordinated use of medical, social, educational and vocational measures.

Table 9.4: Etiology of pediatric handicap

Physical (orthopedic)
<ul style="list-style-type: none"> • Sequelae of fractures, arthritis, etc. • Residual rickets • Chondrodystrophies
Neurologic
<ul style="list-style-type: none"> • Mental retardation • Behavioral/learning disabilities • PPRP • Postmeningitic, encephalitic sequelae • Cerebral palsy • Epilepsy • Degenerative disorders • Birth defects
Sensory
<ul style="list-style-type: none"> • Visual—blindness (partial or complete), refractory errors • Auditory—deafmutism, partial hearing loss • Speech—dysarthria, stuttering, dysphonia
Chronic systemic diseases
<ul style="list-style-type: none"> • Heart disease (both congenital and acquired) • Bronchial asthma • Diabetes mellitus • Malabsorption syndrome • Muscular dystrophy
Social
<ul style="list-style-type: none"> • CAN • Drug addiction • Orphan

Abbreviations: CAN, child abuse and neglect; PPRP, post-polio residual paralysis.

The eventual goal is to reduce the fallout of disabling and handicapping conditions, enabling the individual to actively participate in the mainstream of the community, the so-called **social integration**.

The process of rehabilitation involves:

- Restoration of function (**medical rehabilitation**),
- Restoration of capacity to earn livelihood (**vocational rehabilitation**),
- Restoration of the family and social relationship (**social rehabilitation**), and
- Restoration of personal dignity and confidence (**psychological rehabilitation**).

Naturally, multitudes of subdisciplines are required to participate in this process, including physiotherapy, occupational therapy, speech therapy, audiology, psychology, education, social work, vocational guidance and placement services.

Services for the handicapped must incorporate therapeutics, education, and social and emotional support to the family. Nothing short of community participation can make these services effective. The areas of community participation include:

- Case reporting and referral to the rehabilitative services,
- Raising funds for maintenance of these services,
- Advisory role for planning and administration.

In addition, the community should act as a pressure group for promoting social legislation for the disabled. The community needs to offer employment opportunities in

shops, factories, and other business establishments to the disabled.

Central to all welfare programs is **awareness creation** in the society about the abilities of a child with a handicap. There are many myths about the handicapped. We must put up concerted efforts with support from the mass media (radio, television, press, etc.) to demythify disability and put a thrust on positive approach to child with a handicap.

AVAILABLE WELFARE SERVICES IN INDIA

The following institutes are set up by the GoI as premier institutes in their respective fields to cater to the needs of the handicapped in the area of education, development of manpower, training, vocational guidance, counselling, research, development of suitable service models and low cost aids and appliances:

- National Institute for Orthopedically Handicapped, Calcutta
- National Institute for Mentally Handicapped, Hyderabad
- Ali Yavar Jung National Institute for the Hearing Handicapped, Mumbai
- National Institute for the Visually Handicapped, New Delhi
- Institute for the Physically Handicapped, New Delhi
- National Institute for Rehabilitation, Training and Research, Cuttack.

THE GIRL CHILD

(Gender Bias, Gender Gap, Discrimination against Females)

In India and rest of the resource-poor world, not only the girl child, but the woman as such continues to be discriminated. The sex bias is far more pronounced among the down-trodden and in the rural settings. The discriminated girl child, if she manages to survive, grows up to show discrimination to her female children. This vicious cycle goes on and on and is hard to break.

Currently, we are in the thick of a campaign to generate awareness among people for safeguarding the rights of the girl child and for upliftment of her status. This will eventually have a positive bearing on the status of the woman as well. Every year, **18–24 September** is observed as **girl child week** throughout India.

ISSUES AND PROBLEMS

Female Feticide/Infanticide

Discrimination against the girl child begins even before her birth. The so-called **sex-determination shops** are having roaring business, offering amniocentesis and ultrasound facilities for finding the unborn baby's sex and indirectly instigating abortion of the female fetus. The practice attracts clients from all socioeconomic groups, even if the money has to be begged or borrowed. Birth of a girl is often received with indifference and apathy, at times a reaction akin to mourning.

Now, there is a legal ban on abortion of female fetus following **sex-determination tests**. However, the

144 practice is going on, though illegally, under a garb such as medical termination of pregnancy (MTP). There truly is an unholy nexus between the parents, their advisers, sex-determination clinics and abortionists.

Nutritional Status

On an average, nutritional status of the girl child is poorer than that of the boy. She is more likely to have low birth weight (LBW) and more likely to be given artificial feed. She is provided less amount of food which again is of inferior quality as compared to a boy. Often, it is a practice to postpone onset of puberty in a young girl by restricting her food intake so that parents can buy sufficient time to arrange dowry and a suitable groom for her.

Morbidity and Mortality

The medical needs of the girl child too are ignored. While the biologic truth is that more males die in infancy than females, in India the reverse holds well. The National average for female: male ratio in India in 1981 was 933:1000. It fell down to 929:1000 in 1991, and is estimated to be 927:1000 in 2000.

Educational Status

Educating the girls is hailed as the best investment a nation can make for its bright future. Yet, education of girls in India presents a sordid picture. Quite a proportion of girls never get enrolled in schools. Those who do so show a high rate of dropout. The factors contributing to female illiteracy are listed in Box 9.6. Many parents do not wish to allow girls to get exposed to modern ideas to ensure that they remain docile and submissive. Female illiteracy contributes to innumerable problems related to family welfare.

Girl Child Abuse and Neglect

The girl child is particularly subjected to a considerable exploitation and abuse. She is denied very survival, adequate food intake, education, health care, etc. She is brought up to be submissive and docile, playing second fiddle to the brother. Her attitudes are molded in such a manner that she herself gets gravely biased against her own gender. When she becomes a mother, her treatment to daughters and daughters-in-law becomes a reflection of this unhealthy bias. The custom of *devdasis* and *yallamas* is a sad commentary on the society.

Girl Child Laborer

In India alone, there are around eight million working female children. Out of these, some two million are



Fig. 9.10: Invisible barrier to education. In resource-limited communities, household responsibilities keep millions of girls out of school. To quote the UNICEF, this invisible barrier needs to be broken to assure their right to education.

engaged as domestic servants. Girl child laborers are more exploited than their male counterparts. They are paid less and asked to do more work. This contributes to their poor state of health, nutrition and wellbeing.

Girl Street Child

The girl street child is much worse than her boy counterpart. She is harassed, sexually abused and often pushed into prostitution.

THE SOLUTION/PRACTICAL ACTION PLAN

- There should be no discrimination on the basis of sex. Girls should be given equal opportunities.
- A total ban on female feticide in all States and Union Territories needs to be implemented strictly.
- Awareness of importance of various aspects of the girl child, e.g. education, legal status, etc. needs to be emphasized thoroughly through circulars in various local languages, posters/cartoons at prominent parts of localities, television/radio skits, and street plays, discussions/seminars by local bodies at all levels to ensure participation at grassroots level.
- Education of girls should be the priority—free education of all girls upto secondary school level in all the States of India. Nonformal adult education, especially for women, should be taken up on a war-footing simultaneously.
- Improvement of nutritional status—midday school meal program should be introduced in the municipal and government-aided schools. A special supplementation program should be designed for the severely malnourished children. Vitamin D supplementation should be given as per the need in the community to prevent rickets, especially in girls.
- Compulsory immunization.
- During home visits by the community health workers, stress should be laid on the health status of the girls who may otherwise be neglected by their families.

Box 9.6 Factors influencing female illiteracy

- Cultural, historical and social constraints
- Lack of ample schools
- Lack of female teachers
- An antipathy to coeducation
- Child and teenage marriage
- To participate in household chores (Fig. 9.10).

- Child labor act and laws pertaining to exploitation of children, especially girls, should be revised, simplified and implemented, especially in regard to sexual exploitation.
- Motivation of adoption of girl children and especially handicapped ones needs to be stressed. Mass adoption of girls either from a school or a community by a voluntary organization or an industrial one should also be promoted.
- Handicapped and socially deprived girls should be given job opportunities on a preferential basis.

ACCIDENTS

According to the WHO, an accident is an event, independent of human will, caused by an outside force acting rapidly and resulting in bodily or mental injury. The occurrence of injury is unintended. Majority of accidents are preventable.

MAGNITUDE OF THE PROBLEM

Accidents are undoubtedly among the chief causes of morbidity and mortality in childhood and adolescence in the Western countries. Though in India and other developing countries, the priority health problems are diarrheal disease, malnutrition and infections, accidents too are quite frequent, especially the domestic ones like burns, injuries, poisoning, and traffic mishaps.

MAJOR TYPES

Accidents may be classified into the following five categories:

1. **Accidents requiring medical intervention:** Drowning, burns, falls, cuts and wounds, agroindustrial injuries, animal bites (dogs, snakes, etc.); common poisoning, especially insecticides, rodenticides, kerosene oil and drugs, etc.
2. **Accidents requiring surgical intervention/observations:** Head injuries, burns, soft tissue injuries (faciomaxillary injuries), fractures, trauma to abdominal organs and miscellaneous.
3. **Accidents involving eyes:** Bow and arrow, gulli-danda, fireworks (anar), stone throwing, broom stick and other sticks, sharp-edged toys, balls, shuttle-cocks, fist fighting, fall from a height, knife, scissors, needle, chemical, thermal.
4. **Accidents involving ear, nose and throat (ENT):** Foreign bodies, roadside accidents, corrosive poisoning (kerosene oil), sudden exposure to noise causing sudden deafness, physical injuries (slap), mechanical injuries with sharp objects, strangulation from clothes being entangled in rotary machines, automobiles, etc. kite-flying, causing laryngotracheal cuts, loss of pinna, etc.
5. **Road/traffic accidents:** Reversing car, careless road crossing, playing in streets with vehicular traffic, allowing children to stand in a car, or, still worse, to sit in driver's lap.

PREVENTIVE MEASURES

Accident prevention needs three things. **First** is the forethought which means to anticipate the possible risk to the child. **Second** is time in order to watch the child and his activities. **Third** is discipline which should be well balanced.

EDUCATION

Education can play as great a preventive role in accidents as vaccination in disease prevention. It should be imparted to the parents, school teachers and grown-up children.

STRICT IMPLEMENTATION OF RULES

Traffic rules, such as compulsory wearing of crash helmets, restriction of speed to recommended limits, checking of blood alcohol level of drivers and regular checking of vehicles, etc. must be strictly enforced. It is suggested that seat belts should also be made compulsory for car riders—the driver and the user of the front seat, in particular. Also, regular caution needs to be exercised in issuing driving licenses. A driving license should bear the blood group of the owner.

Children must not travel in the front seat of the car. Condition of roads must be upto the mark.

Every crossing and every vehicle must have first-aid facilities and every driver must be familiar with first-aid administration before being issued a license.

ELIMINATION OF CAUSATIVE FACTORS

Reduction in accidents can be successfully attained by eliminating the factors that are likely to cause them. The remedial measures in this behalf can be in the form of improvement of housing, safe storage of drugs and poisons, improvement of roads and proper placement of electric points, etc.

MEDICAL CARE OF THE VICTIM

Many deaths can be prevented if accident victims are provided emergency care at the accident site, during transportation and in the hospital emergency room.

- Police must not harass people who contribute in transporting an accident victim to the nearest hospital or doctor.
- It is advisable to provide traffic constables, a two way walkie-talkie to speed up the process of medical help.
- Every medical college must have a comprehensive trauma care and rehabilitation unit.

SURVEY AND RESEARCH

Studies need to be undertaken about the causes, extent, type and other characteristics of accidents as also determining new ways and means of making the environment safer and changing human behavior for controlling accidents.

CHILD ABUSE AND NEGLECT

The spectrum of child maltreatment encompasses acts of abuse or commission and acts of omission or neglect/lack of appropriate action by a caretaker, resulting in adverse effects and even mortality in children. The following factors

146 contribute to higher incidence of such maltreatment in groups living in poverty:

- Enhanced number of crises in their lives in the form of unemployment, overcrowding and disease.
- Limited reach to social and economic resources for support during times of stress.
- High rate of violence, teenage pregnancy, single parenthood and drug abuse (all risk factors).
- Higher reporting because of more scrutiny by social agencies.

Discussed in details elsewhere *See* Chapter 6 (Developmental, Behavioral and Psychiatric Disorders), the malady needs to be fought by a multipronged strategy, including awareness activities. The IAP Committee on child abuse, neglect and child labor (CAN-CL) and other such organizations are engaged in developing and executing such programs.

INDIA'S NATIONAL HEALTH PROGRAMS

Various national health programs, currently in operation in India, are listed in Box 9.7.

REPRODUCTIVE AND CHILD HEALTH (RCH PROGRAM)

This program followed revisions in the child survival and safe motherhood (CSSM) program as per the recommendations made at the International Conference on Population and Development in Cairo in 1994 and was born in 1997. Its goals are removing all targets for family planning, phasing out incentive payment to both providers and acceptors of family planning methods, increasing utilization of existing facilities and using the voluntary and private sector to enhance access to services and fill gaps left by public sector providers. RCH program is a target-free program with voluntary participation. The package of services offered by RCH program is:

Box 9.7 India's National Health Programs

- National Malaria Eradication Program
- National Family Welfare/Planning Program
- National Tuberculosis Control Program
- National Leprosy Control Program
- National Filariasis Control Program
- Iodine Deficiency Control Program
- National Water Supply and Sanitation Program
- National Program for Prevention of Visual Impairment and Control of Blindness
- Diarrheal Disease Control Program
- STD Control Program
- Universal Immunization Program
- Minimum Need Program
- 20-Point Program
- Guinea worm Eradication Program
- National Diabetic Control Program
- National AIDS Program
- CSSM Program
- RCH Program.

Abbreviations: STD, sexually transmitted disease; CSSM, child survival and safe motherhood; RCH, reproductive and child health; AIDS, acquired immunodeficiency syndrome.

For the Children

- Essential newborn care
- Exclusive breastfeeding
- Immunization
- Appropriate management of acute respiratory infection (ARI)
- Vitamin A prophylaxis
- Treatment of anemia.

For the Mother

- Tetanus toxoid (TT) immunization
- Prevention and treatment of anemia
- Antenatal care and early identification of maternal complications
- Deliveries by trained personnel
- Promotion of institutional deliveries
- Management of obstetrical emergencies
- Birth spacing.

For the Eligible Couples

- Prevention of pregnancy
- Safe abortion.

For Reproductive Tract Infection (RTI)/Sexually Transmitted Diseases (STDs)

Prevention and treatment of RTI and STDs.

INTEGRATED MANAGEMENT OF NEONATAL AND CHILDHOOD ILLNESS (IMNCI STRATEGY)

INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESS (IMCI)

This WHO/UNICEF designed strategy is inspired by the common observation that in developing countries illness usually strikes as a group rather than as a single disease, say diarrhea or respiratory infection. In addition, anemia, malnutrition and poor immunization coverage often go unaddressed although these are known to commonly accompany these illnesses. Here, therefore, the focus in an integrated manner is on main causes of morbidity and mortality as also the overall health of the child.

Major Components

Three remarkable components of the strategy are:

1. Improvement of case management skills of health providers through provisions of locally adapted guidelines and training activities to promote their use. Guidelines on referral criteria are quite an important component of the algorithm.
2. Provision of essential drug supplies required for effective case management of childhood illness.
3. Optimization of family and community practices in relation to child health, particularly care-seeking behavior.

INTEGRATED MANAGEMENT OF NEONATAL AND CHILDHOOD ILLNESS (IMNCI)

In India, IMCI has been expanded to include neonatal care. Hence, it is rechristened integrate management of neonatal

and childhood illness (IMNCI) and made the central pillar of the child health strategy under RCH-II/NRHM.

Major Components

- Improvement in case-management skills of health staff through appropriate guidelines.
- Improvement in the overall health system.
- Improvement in family and community healthcare practices.

Types of IMNCI

- **Pre-service IMNCI:** Inclusion of IMNCI in the curriculum of medical colleges in India.
- **Facility-based IMNCI (F-IMNCI):** Provision of suitable inpatient management of major causes of neonatal and childhood mortality.
- **Newborn care corner (NBCC):** A mandatory space within delivery room of all health facilities conducting deliveries to provide immediate care to all newborns at birth.
- **Newborn stabilization unit (NBSU):** A four bedded unit and two beds in postnatal ward for rooming in are mandatory within or close to the maternity ward. Here sick and LBW infants can be cared and stabilized for brief periods.
- **Special newborn care unit (SNBCU):** It is a requirement for any facility with more than 3,000 deliveries/year and consists of a neonatal unit in the vicinity of labor room to provide special care for sick neonates.
- **Triage of sick newborns:** Newborns are classified as **emergency** (requiring urgent intervention and emergency measures). **Priority** (sick needing rapid assessment and admission to SNCU stands for Special Neonatal Care Unit) and **non-urgent** (though urgent attention not needed, they are in need of further assessment and counseling).

Principles of IMNCI Guidelines

- All sick young infants upto two months of age must be assessed of possible bacterial infection/jaundice and diarrhea.
- All sick children aged two months upto five years must be examined for **general danger signs** and then for cough or difficult breathing, diarrhea, fever or ear problems.
- All sick young infants and children aged two months upto five years must also routinely be assessed for nutritional and immunization status, feeding problems and other potential problems.

Only a limited number of carefully-selected clinical signs of high sensitivity and specificity are used. Based on the signs, the child is assigned to color-coded classification, i.e. **pink** suggests hospital referral/hospitalization; **yellow** indicates specific treatment and **green** calls for home treatment.

Guidelines address most but not all health problems. Management procedures use a limited number of essential drugs and encourage active participation of caretakers

who need counseling about home care, including feeding, fluids and follow-up visit(s). **147**

Steps of Management

- **Step 1:** Check-up to identify the illness
- **Step 2:** Classification of illness according to color-coded charts
- **Step 3:** Advice retreatment/referral/home management (including counseling)
- **Step 4:** Follow-up.

Facility-based Integrated Management of Childhood Illnesses

F-IMNCI is the integration of facility based care of sick newborn and children with IMNCI to empower health professionals with skills to manage common newborn and childhood illnesses at the community as well as facility level.

It mainly focuses on providing appropriate skills for inpatient management of:

- Major causes of neonatal and childhood mortality like asphyxia, sepsis, low birth weight in neonates; and
- Pneumonia, diarrhea, measles, malaria, meningitis, and acute severe malnutrition in children.

It allows a continuum of good quality care to sick newborns and children.

BABY-FRIENDLY HOSPITAL INITIATIVE

The baby-friendly hospital initiative (BFHI) aims at making hospitals more supportive of a primary health care approach. Such a focus on hospitals is the outcome of inappropriate health care practices that have developed in the past. There is evidence that practices (wrong or right) followed in hospitals have a multiplier effect that set examples for health practitioners in the community.

A baby-friendly hospital is a hospital that follows the WHO/UNICEF code of practice which sets out the **ten steps to successful breastfeeding** (Box 9.8).

The **baby-friendly hospital** campaign was launched by the WHO and UNICEF in mid 1991 in Ankara (Turkey),

Box 9.8

World Health Organization(WHO)/United Nation's Emergency Fund (UNICEF) ten steps to successful breastfeeding

1. Have a written breastfeeding policy-routinely communicated to all health staff.
2. Train all health staff in skills to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within half an hour of birth.
5. Show mothers how to breastfeed, and how to maintain lactation even if they should be separated from their infants.
6. Give newborn infants no food or drink other than breast milk, unless medically indicated.
7. Practise rooming in (allow mothers and infants to remain together) 24 hours a day (Fig. 9.11).
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers (also called dummies or soothers) to breastfed infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.



Fig. 9.11: Mothers and newborns should be kept together 24 hours a day from birth.

to boost breastfeeding and to counter the worldwide trend towards bottlefeeding. The philosophy behind this new strategy is that hospitals set the standards for primary care and act as the major providers and trendsetters, thereby influencing the behavior of the health providers and the community. What is practiced in hospitals is viewed by community at large as the right thing to do. Making hospitals baby-friendly could, therefore, contribute considerably to curb the trend in favor of bottle feeding and promoting breastfeeding.

The movement that took off in 1991 in 12 countries has now become global. Experience has shown that the following benefits in such hospitals are immediate, obvious and substantial:

- Decrease in infection rate.
- Improved survival of LBW infants.
- Easing of the hospital burden due to vast savings on infant formula purchase.
- Reduction in nursing load as rooming in and demand feeding make nursery care easier.

In India, hospitals are still in the stages of joining this movement. The procedure consists of a candidate hospital improving practices to the point that it follows the **ten steps** faithfully. Training the health care providers for successful implementation of the ten steps is an important input.

Besides promotion of breastfeeding, baby-friendly hospital initiative in India also proposes to provide:

- Improved antenatal care
 - Mother-friendly delivery services
 - Standardized institutional support of immunization
 - Diarrhea management
 - Promotion of healthy growth and good nutrition
 - Widespread availability and adoption of family planning.
- The baby-friendly hospital initiative has proved an initial step to make hospital facilities more friendly to mother, baby and child. The momentum is gradually picking up.

SCHOOL HEALTH SERVICE

School-going period is relatively safe from health point of view. However, supervision of the health of school children is important. Sound health and its care picked up during these years have a great bearing on the individual, his family and the community for years to come.

PRIORITY HEALTH PROBLEMS

Major health problems of school children needing special attention include:

- Nutritional deficiency states with special reference to mild-to-moderate PEM, nutritional anemia, xerophthalmia, etc.
- Infectious diseases,
- Intestinal parasitic (both protozoal and helminthic) infestations,
- Dental caries,
- Skin diseases,
- Eye diseases,
- Ear diseases.

AIMS AND OBJECTIVES

- Promotion of positive health
- Prevention of disease
- Timely diagnosis, treatment and follow-up
- Health education to inculcate awareness about good and bad health
- Availability of healthful environments.

SALIENT COMPONENTS/FEATURES

- Health appraisal
- Remedial measures and follow-up
- Prevention of communicable diseases
- Healthful environment
- Nutritional services
- First-aid facilities
- Mental health
- Dental health
- Eye health
- Ear health
- Health education
- Education of handicapped children
- School health record.

An important component of school health program is training the teachers in the basic concepts of hygiene, nutrition, prevention and early detection of morbidities. Teachers can also act as liaison agents between children and health care providers.

JUVENILE DELINQUENCY

Unlawful activities and offences committed by teenagers (boys less than 18 years, girls less than 16 years), though with psychiatric background and implications, need to be considered from social point of view as well.

Etiology includes:

- Biologic causes
 - Psychiatric disorders
 - XYY chromosomal pattern.
- Social causes
 - Broken homes
 - Environmental influences
 - Lack of proper recreational facilities
 - Over exposure to thrillers on television (TV) and theater.

Prevention lies in improvement of family life, better schooling and social welfare services. Also See Chapter 6 (Developmental, Behavioral and Psychiatric Disorders).

INDIA'S NATIONAL NUTRITION PROGRAMS

See Chapter 11 (Nutritional Requirements).

INDIA'S NATIONAL NUTRITION POLICY

See Chapter 13 (Malnutrition).

ADOPTION

See Chapter 6 (Developmental, Behavioral and Psychiatric Disorders).

ACUTE FLACCID PARALYSIS (AFP) SURVEILLANCE

The strategy aims at identifying cases of AFP (polio, Guillain-Barre syndrome, transverse myelitis, and traumatic neuritis) and reporting them to the District Immunization Officer of the area for further action. For details, See Chapter 18 (Viral Infections).

TELEVISION AND THE CHILD

A BOON

Undoubtedly, TV has become a part and parcel of our life. Like adults, children too watch it for entertainment, information, reassurance and comfort after stressful experience, overcoming boredom, etc. Educational TV programs can enhance the cognitive development of children, especially the preschoolers, in reading, readiness and acquisition of vocabulary. For older children, it is an excellent source of current events, science, history and politics. Suitably chosen programs are capable of supplementing parents' activities aimed at inculcating knowledge, skills, information and motivation for learning.

AGE-WISE TV VIEWING

Experience has shown that children start consistent TV viewing between 2 and 3 years of age.

- A child of 4–5 years may not be able to fully understand a program, but he does form some impression of what he has viewed. Of course, he cannot differentiate between fantasy and real happening clearly. To him everything on TV is true to life. A violent scene could be as terrifying to him as violence in real life.
- Between 8 and 12 years of life, child's understanding of TV improves considerably. Now, he is able to draw conclusion from certain programs. There is a considerable improvement in memory for program contents.
- The adolescent has a tendency to become increasingly critical of the TV programs. He, therefore, becomes choosy too.

ADVERSE EFFECTS

Among the probable adverse effects of excessive or erratic TV viewing ranks the following:

- Infringement on child's time meant for studies, play, sports and hobbies, etc.
- Much-too-much of snack-eating during TV watching and reduction in activity, resulting in obesity.



Fig. 9.12: Television and the child. The onus for choosing proper TV programs for the child lies on parents' judgement.

- Adolescent delinquency and violence secondary to viewing of violent TV programs.
- Behavioral problems secondary to violent, horror or adult programs.

THE WAY-OUT

- Parents must use their balanced judgment in choosing TV programs for the child (Fig. 9.12).
- Parents must assist children through interaction to drive sensible and positive interpretations from the programs watched by them.
- Parents must introduce children to hobbies and alternate channels of recreation so that they build relationship to the world around them rather than to the TV set.
- Schools should play a positive role in utilizing creative and beneficial aspects of TV. Recognizing the value of TV as the third parent, the IAP is striving to have a Kaleidoscopic Innovative Doordarshan (KID) channel which would exclusively present programs that children like to see and which parents, teachers and caretakers want children to see.

UNDER-FIVE CLINICS

BACKGROUND

The modified well-baby clinic of the West that blends preventive as well as curative activities for preschool children has been called the under-fives or young child clinic in the developing areas of the world.

The concept of such clinics originates from the fact that an overworked rural mother cannot carry her healthy 6 months old infant to one type of clinic for vaccination and a 3-years-old child—suffering from some ailment to another center.

WHY SUCH AN EXCLUSIVELY PREFERENTIAL STRESS ON THE UNDER-FIVES?

- **Firstly**, they are a special-risk group needing particular health care. They constitute 17% of the country's total population, but account for as high as 50% of the total

- 150 deaths, the major causes of morbidity and mortality being malnutrition, infections and diarrheal disease.
- **Secondly**, common illnesses of this age group—say malnutrition, infections, diarrheal disease, accidents, etc—are all preventable.
 - **Thirdly**, this age period is known for its accelerated growth and development, warranting regular monitoring.
 - **Fourthly**, this age group needs special inputs so that children are brought into the orbit of special health care.

SERVICES RENDERED

The services rendered by the clinic are set out in the symbol for the under-fives clinics (Fig. 9.13).

- The **apex of the large triangle** represents care in illness by a trained health worker.
- The **left triangle** represents adequate nutrition. The health worker attempts to identify early onset of growth failure and malnutrition through the road-to-health card, provides supplementary nutrition and gives necessary nutritional education to the mothers.
- The **right triangle** represents immunization, indicating coverage of at least the six diseases—tuberculosis, polio, diphtheria pertussis, tetanus and measles—and, if possible, typhoid as well under the universal immunization program (UIP), formerly designated expanded program on immunization.
- The **central triangle** represents family planning. The aim is to give to the mother all the advice about family planning. The border across the symbol represents health teaching to the mother through posters, charts, sketches and diagrams, etc.

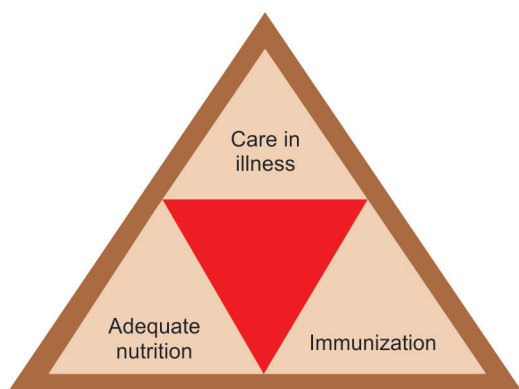


Fig. 9.13: Symbol for under-fives clinic. Central triangle (red) represents family planning. The line bordering the big triangle represents health teaching to the mother.

OPERATIONAL MODALITIES

- The under-fives clinic is usually located in a village, a slum or a labor colony.
- It is managed by a health worker trained in child health and nutrition. She gives nutritional education to the mothers, weighs the children at least once a month and immunizes them against infectious diseases.
- The health worker also makes home visits to educate the mothers and to make sure that they care to bring their children to the clinic for regular check-up.
- At times, such clinics also provide low-cost weaning foods to fight impending malnutrition in the preschoolers.

DISPOSAL OF HOSPITAL WASTE

According to the Biomedical Waste (Management and Handling) Rules 1995, the biomedical wastes are to be handled as per the prescribed procedures. These procedures specify authorization/responsibility of generators and operators, segregation, packaging, transportation and storage, treatment and disposal, maintenance of records and returns, accident reporting and follow-up, and import and export methods for biomedical wastes.

All hospitals and nursing homes are required to install incinerators/suitable devices for safe disposal of human anatomical waste (tissues, organs, and body parts), blood and body fluids and items saturated or dripping with blood and body fluids (Fig. 9.14). The authority for execution of the provisions is entrusted to the state pollution control boards.

Segregation of waste in color coded bags

Yellow bags	Red bags	Blue bags	Black Carboy
Infectious waste, bandages, gauzes, cotton or any other things in contact with body fluids, human body parts, placenta	Plastic waste such as catheters, injections, syringes, tubings, intravenous bottles	All types of glass bottles and broken glass articles, outdated and discarded medicines	Needles without syringes, blades, sharp and all metal articles

Fig. 9.14: Disposal of hospital waste. Note the color-coded bags for segregation of waste.

Multiple Choice Questions

1. Which of the following is the most appropriate statement in relation to community pediatrics?
 - A. ICDS scheme also covers expectant and nursing mothers
 - B. Poverty is the single most important factor contributing to child labor
 - C. Every year, 18–24 September is observed as girl child week throughout India
 - D. All of the above
2. Spot the wrong observation:
 - A. Health is a state of complete physical, mental and social wellbeing, and not merely an absence of disease or infirmity
 - B. The term, community pediatrics, refers to the practice of pediatrics only outside the hospitals

contd...

- C. Preventive pediatrics is meant prevention of disease and promotion of physical, mental and social wellbeing of children with the aim of attaining a positive health
- D. **Tertiary prevention:** Halting development of disabilities from an established disease
3. All the following are part of Baby Friendly Hospital Initiative, except:
- Artificial feeding if the mother fails to have lactation by 12 hours
 - Rooming in for 24 hours
 - Breastfeeding on demand rather than time schedule
 - Only breastmilk for newborns
4. True entries about National Family Health Mission include all the following, except:
- It has been in active functioning since 2005
 - Since 2010, it has been augmented with Reproductive, Maternal, Newborn, Child and Adolescent Health (RMNCH+ A) strategy
 - It is India's flagship program for the community
 - It is in operation in two major forms, namely National Rural Health Mission (NRHM) and National Urban Health Mission (NUHM)
5. Each of the following observations about IMNCI is correct, except:
- It is an expansion of IMCI in India
 - Newborn care corner (NBCC):** A mandatory space within delivery room of all health facilities conducting deliveries to provide immediate care to all newborns at birth
 - Step 1 in management pertains to classification of illness according to color-coded charts
 - All sick young infants up to two months of age must be assessed of possible bacterial infection/jaundice and diarrhea

Answers

1. A 2. B 3. A 4. B 5. C

Clinical Problem-solving

Review 1

An 18-month-old girl, weighing 6 kg, presents with cough and cold for 2 days in a primary health center. On examination she is alert with a respiratory rate of 38/minute but without chest indrawing and temperature of 36.2°C. Though she has visible severe wasting, there is no pedal edema and no pallor.

- What is your assessment as per IMNCI?
- What should be the immediate treatment
- How will you manage this patient in a health facility?

Review 2

A 9-year-old street boy, unimmunized except for BCG, is brought to the clinic for routine checkup by a NGO.

- What are various problems/diseases you anticipate in such a child?
- How will you plan vaccination schedule for this child?

Answers

Review 1

- This infant has cough or cold which appear to be consistent with diagnosis of upper respiratory tract infection. There is no evidence of pneumonia or bronchiolitis. However, severe malnutrition is present.
- Child needs referral for hospitalization in a higher center. However, in view of severe malnutrition, she needs pre-referral treatment in the form of a single dose of vitamin A, prevention of low blood sugar and maintenance of temperature as per IMNCI norms.
- For appropriate management at the higher center, the ten step management of severe acute malnutrition (SAM) should be followed.

Review 2

- Street children are at an increased risk of developing nutritional deficiencies, tuberculosis, sexually transmitted disease (STDs), human immunodeficiency virus (HIV) infection, substance abuse, skin disorders, intestinal parasitic infestations, prostitution and criminal exploitation.
- When planning vaccination of an unimmunized child we need to keep in mind various vaccine preventive diseases prevalent in that particular age group. Children presenting late for vaccination should be immunized at first contact (preferably) as the passive immunity derived from maternal antibodies gradually wanes. Indian Academy of Pediatrics has given recommendations for vaccination of unimmunized children (Table 9.5).

Table 9.5: Vaccination of unimmunized children as per IAP

Visit	Suggested vaccines
First	Measles (MMR if more than 12 months) DTwP1/DTaP1 (Tdap if 7 years or more) OPV1/IPV1 (only if less than 5 years) Hib 1 (Only if less than 5 years) Hep B 1
Second visit (after 1 month of first visit)	BCG (only in less than 5 years) DTwP2/DTaP2 (Td if 7 years or more) OPV 2 (if OPV given earlier) Hep B 2 Hib 2 (if less than 15 mths)
Third visit (after 1 month of second visit)	OPV3/IPV2 MMR (if more than 12 months) Typhoid (if more than 2 years)
Fourth visit (6 months after first visit)	DTwP3/DTaP3 (Td if 7 years or more) OPV4/IPVB1 HepB3

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OVERVIEW

Ever since the discovery of smallpox vaccine in 1798 by Edward Jenner, spectacular advances have occurred from time to time in the form of an umbrella of highly effective vaccines to provide safeguard against the onslaught of infectious diseases (Fig. 10.1). Today, immunization programs, perhaps the most cost-effective and productive health investment, form the sheet anchor of the preventive services. These aim at preventing disease by producing controlled clinical reactions which are likely to confer effective and, as far as possible, lasting resistance to infections, the so-called **immunity**.

Box 10.1 lists the important milestones in immunization in India. All along immunization has remained a key component of various child-centric programs in India, say Children's Special Service Mission (CSSM), Reproductive and Child Health (RCH), National Rural Health Mission (NRHM) and National Urban Health Mission (NUHM) with support from global agencies such as World Health Organization (WHO), Global Alliance for Vaccines and Immunization (GAVI) and Global Vaccine Action Plan (GAVP). India's national vaccine Policy is guided and revamped in the wake of changing needs and new knowledge by the National Technical Advisory Group on Immunization (NTAGI).



Fig. 10.1: Immunization. The pathbreaking revolution. Immunization has been rightly hailed as “the greatest discovery of the times for prevention against infectious diseases”.

Box 10.1 Milestones in immunization in India

- **1978:** WHO's EPI, already in operation since 1974, was adopted by India. Six vaccines—BCG, polio (OPV), DTP and typhoid were covered under EPI
- **1985:** UIP was launched to boost immunization coverage beyond infancy in India with two changes:
 - Exclusion of typhoid vaccine
 - Inclusion of measles vaccine.
- **1990:** Vitamin A supplementation was introduced in the UIP
- **1995:** PNIDs introduced
- **2002:** Hepatitis B vaccine introduced in 2002 in some States
- **2011:** Hib plus hepatitis B plus DTP vaccine (pentavalent vaccine) introduced in some States
- **2014:** MMR introduced.

Abbreviations: WHO, World Health Organization; EPI, expanded program of immunization; BCG, Bacillus Calmette–Guérin; OPV, oral poliovirus vaccine; Hib, hemophilus influenza type B; DTP, diphtheria, pertussis and tetanus; UIP, universal immunization program; PNIDs, Polio National Immunization Days; MMR, measles, mumps and rubella.

Unfortunately, notwithstanding established value of immunization, effective vaccines are not being used on a scale that is needed to provide tangible results. Studies clearly indicate that the immunization status of our pediatric population is as yet far from adequate. Surely enough, the picture in other developing countries is not significantly different. This explains why, while in affluent countries infectious diseases have gone down in the mortality list, these continue to be a major factor for morbidity and mortality in the resource-limited world.

India is engaged in boosting immunization coverage of children to safeguard them from vaccine preventable diseases through various endeavors. Government of India's newly launched **Indradhanush Mission** aims to cover all those children who are unvaccinated or are partially vaccinated against seven vaccine preventable diseases which include diphtheria, whooping cough, tetanus, polio, tuberculosis, measles and hepatitis B, by the end of the year 2020.

Immunize India, a national non-profit initiative, promoted by the Indian Academy of Pediatrics (IAP) is the world's largest vaccination reminder service. Immunize India services are available free of cost to parents anywhere in India. Parents opt into the service by sending a text message by SMS to the national short code 566778 from any mobile phone in India. Three reminders are sent, at two day intervals, for each vaccination that is due. About seven lakh families have already benefited from this service. The program has been receiving international recognition and several regions/countries now want to adopt or develop similar services.

Vaccination and immunization, though interchangeable in practice, are not exactly synonymous.

VACCINATION

- It is the process of inoculating the antigen (vaccine) into the body, regardless of its **seroconversion**, i.e. change from antibody negative to antibody positive.
- It is not the same as **seroprotection** which is the actual state of protection from infection as a consequence of development of antibodies from seroconversion.
- The vaccine contains one or more antigens of a pathogen (usually a virus or bacteria) plus adjuvants (say aluminium hydroxide, lipids) which enhance its ability to elicit a cellular, humoral or combined immune response (immunogenicity).
- It is expected to elicit an immune response not amounting to disease. The response is largely humoral as in hemophilus influenza type b (Hib) vaccine, cellular as in Bacillus Calmette-Guérin (BCG) or both as in a majority of the vaccines.

Two terms, **vaccine efficacy** and **vaccine protective-ness**, need clarification.

Vaccine Efficacy

The term, **vaccine efficacy**, denotes an ability of the vaccine to protect against infection and is epidemiologically expressed by the formula:

Vaccine efficacy =

$$\frac{\text{Rate of infection in unvaccinated population} - \text{Rate of infection in the vaccinated population}}{\text{Rate of infection in unvaccinated population}}$$

Vaccine Effectiveness

The term, **vaccine effectiveness**, refers to an ability of the vaccine to protect the population from infectious disease. Three factors that influence vaccine effectiveness are:

1. Vaccine efficacy
2. Implementation of the immunization program
3. Herd immunity/effect. Passing on the benefit of protection to even the unimmunized population is termed **herd immunity or effect**. Oral polio vaccine (OPV) followed by measles vaccine are the outstanding examples of this phenomenon.

IMMUNIZATION

Immunization is the process of inducing immune response, humoral or cell-mediated, in the body so that protection is provided against infection. It may be active (antigen is introduced so that it produces protective antibodies), or passive (readymade antibodies are introduced). **Primary immune response** occurs when an antigen is introduced for the first time and the immune system responds primarily after a lag phase of upto 10 days. Besides lag phase, primary response is short-lived, predominantly IgM type and has low titer. **Secondary immune response** occurs on reintroduction of the same antigen. There is no lag phase. The immune system responds by producing antibodies immediately. On

a nutshell, secondary response is immediate, long-lasting, and has a very high titer.

Immune response may be:

- **T cell dependent**, involves both T cell and B cell. It is prompt, IgG type, long-lasting with high titer and shows booster effect with repeated exposures. It also reduces carrier state because of production of IgA. After 6 weeks of age, this response is evident.
- **T cell independent** response is only B cell mediated. It is mainly IgM type, short-lived, shows revaccination rather than booster effect and does not reduce carrier state. It occurs after two year of age only.

Conjugation is a technique whereby T cell independent antigen (polysaccharide) can be made into T cell dependent. The conjugated vaccine can be given under two years of age. Examples: Conjugated Hib, pneumococcal, Vi typhoid and meningococcal vaccines.

Furthermore, immunization may be active or passive.

Active immunization denotes introducing antigen that leads to production of protective antibodies in order to provide protection from future infection. On the other hands, in **passive immunization**, readymade antibodies (performed in another host) are injected during the incubation period of an infectious disease to restrict viral multiplication and, thereby, provide immediate defense/protection. Administration of specific immunoglobulin or nonspecific normal human immunoglobulin as in case of hepatitis A (hep A) and measles provides passive protection against these viral infectious illnesses.

In **active-passive immunization**, both active immunization *via* a vaccine (antigen that stimulates production of antibodies) for providing long-term protection and passive immunization *via* immunoglobulins (performed antibodies) for providing immediate protection are given. Preventing hepatitis B (hep B) as well as tetanus is its best illustrative examples.

Salient details of various vaccines are described later in this chapter. Table 10.1 lists important features of various immunoglobulins, and Table 10.2 represents antisera and antitoxins for passive immunization.

Categories of Vaccines

- **Live attenuated vaccines (LAVs):** In genetically engineered attenuation, virulence determining gene is deleted, e.g. typhoid and cholera vaccines. LAVs are capable of replicating within the body and stimulating immune response. As a rule, usually a single dose should be good enough for long-term immunity. They can, though rarely, become virulent and cause disease per se. These are contraindicated in immunocompromised states.
- **Killed inactivated vaccines:** They do not multiply in the body and need to be given in multiple primary and booster doses. Additionally, there are two more types of vaccines—toxoids and subunit vaccines.
 1. **Toxoid-based vaccines:** Here a modification to purify the toxins is affected so that benefit of

Table 10.1: Immunoglobulins for passive immunization

Infectious disease	Indications	IM dose	Remarks
Measles	• Infant aged less than 1 year provided exposure is less than 6 days.	0.25 ml /kg	Normal human globulin
	• Immunocompromised state (including pharmacotherapy-induced).	0.5 ml /kg	Normal human globulin
Hepatitis A	• Hepatitis outbreak in an institution/group.	0.02 ml /kg	Normal human globulin
	• Exposure to a hepatitis A infected subject.	0.02 ml /kg	Normal human globulin
	• Travellers to endemic areas of hepatitis A.	0.02 ml /kg; to be repeated every 4 monthly in case of prolonged travel in endemic area	Normal human globulin
Varicella (chickenpox)	• Newborns of infected mothers developing lesions within 6 days of birth.	12.5 IU/kg with a maximum of 625 IU	Specific hyperimmune globulin
	• Infant aged less than 1 year. • Immunocompromised with exposure of less than 6 days.	– Do – – Do –	– Do – – Do –
Tetanus	• Wound/exposure in unimmunized/incompletely immunized subjects.	250 units	Specific hyperimmune globulin
	• As treatment.	300–6000 units	– Do –
Rabies	Rabid animal bite	20 units/kg	Specific hyperimmune globulin

Abbreviations: IU, international units; IM, intramuscular.

Table 10.2: Antisera/antitoxin for passive immunization

Antisera/antitoxin	Indications	IM dose
Diphtheria antitoxin	Susceptible contact	500–1000 units
ATS	Wound/exposure in unimmunized/incompletely immunized subjects	1500 units
Rabies antiserum	Rabid animal bite	40 IU/kg

Abbreviations: ATS, anti-tetanus serum; IU, international unit; IM, intramuscular.

protection becomes available and yet it does not become harmful to the subject. Such a vaccine needs to be given in several divided doses to cut down adverse events. Moreover, booster doses are mandatory to sustain protection.

2. **Subunit vaccines:** These are nonreplicating antigens. Important ones are:
 - Capsular polysaccharides
 - Viral subunits
 - Bacterial subunits.

By stimulation of B cells, subunit vaccines elicit humoral response. Only IgM antibodies are produced by these vaccines. Table 10.3 lists various vaccines that are currently recommended.

COLD CHAIN

DEFINITION

Cold chain is a system of storing and transporting vaccines at low temperature from the manufacturer to the actual vaccination location, so that their potency and efficacy are preserved.

Table 10.3: Classification of vaccines

Type	Vaccines falling under the umbrella
Bacterial vaccines <ul style="list-style-type: none"> • Live(attenuated) • Killed (inactivated) 	BCG, typhoid (oral, i.e. Ty21)
Viral vaccines <ul style="list-style-type: none"> • Live (attenuated) • Killed (inactivated) 	DTwP, typhoid (whole-cell killed)
Toxoids	Polio (Sabin), i.e. OPV, Measles, MMR, varicella, rotavirus, yellow fever
Subunit vaccines	Polio (Salk), i.e. inactivated polio vaccine, rabies, hepatitis A, influenza (only whole virion)
	Diphtheria, tetanus toxoids
	Bacterial—acellular pertussis (aP)
	Viral—hepatitis B (recombinant), influenza (only split)

Abbreviations: BCG, Bacillus Calmette–Guérin; DTP, diphtheria, pertussis and tetanus; HHE, hypotonia-hyporesponsive episode; OPV, oral polio vaccine; IPV, inactivated polio vaccine; Hib, Haemophilus influenzae type b; GBS, Guillain-Barre syndrome; VAPP, vaccine-associated paralytic polio; GI, gastrointestinal.

A failure of cold chain may result in inadequate or negligible protection against the disease despite vaccination. The reports of occurrence of vaccine preventable diseases in populations considered to be adequately immunized through vaccination appear to be related to cold chain failure.

THREE PILLARS

Three vital elements in successful cold chain are:

1. Cold chain equipment
2. Transportation
3. Motivated and trained manpower for maintaining the link.

Table 10.4: Recommendations on storage of vaccines in the refrigerator

Compartment	Vaccines
Freezing	OPV
Main <ul style="list-style-type: none"> • Top • Middle • Lower 	BCG, measles, MMR, mumps DTP, TT, Hep A, Hep B Diluent

Abbreviations: OPV, oral polio vaccine; BCG, Bacillus Calmette–Guérin; MMR, measles mumps and rubella; DTP, diphtheria, pertussis and tetanus; TT, tetanus toxoid.

EQUIPMENT

The cold chain equipment consists of:

- **Cold box:** This can transport large quantities of vaccines by vehicle to outreach sites, preserving the vaccine for upto 1 week without any power supply at all.
- **Vaccine carrier:** This is designed to transport small quantities of vaccine by a vehicle, bicycle or on foot to outreach sites, preserving the vaccine for upto 3 days.
- **Flask:** This is only a substitute for carrier, but should not be much encouraged.
- **Ice-packs:** These are employed for use in box, carrier or flask.

Table 10.4 gives guidelines regarding storage of vaccines for prolonged life in a refrigerator. Note that storing OPV in deep freezer with a temperature of minus 20°C. Enhances the life of the vaccine from 3 months–6 months.

ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFI)

(Adverse Vaccine Reactions, Vaccine-associated Adverse Events)

According to the WHO, an AEFI is a transient adverse reaction supposed to be caused by immunization/vaccine. Though the untoward event may be associated with the vaccine, it may not necessarily be the result of it.

CATEGORIES

AEFI may be categorized as per Box 10.2. All AEFIs are required to be reported to the appropriate authorities.

AEFI IN RELATION TO INDIVIDUAL VACCINES

AEFIs in relation to various vaccines are listed in Box 10.3.

PREVENTION

- It must be ensured that the vaccine being administered has undergone recommended cold chain, storage, and handling, and is upto the mark as per vaccine vial monitor (VVM) as and when available.
- In addition to following manufacturer's instructions, it should be ascertained that the right technique (route, needle size, and site of injection) is adhered to.

Box 10.2

Categories of adverse events following immunization (AEFI)

- **Vaccine reaction:** Adverse event caused or precipitated by the vaccine when given correctly; caused by the inherent properties of the vaccine.
Examples: Anaphylaxis, vaccine-associated polio paralysis (VAPP).
- **Program error:** Event caused by an error in vaccine preparation, handling, or administration.
Example: Toxic shock syndrome in case of measles vaccine.
- **Injection-related reaction:** Event from anxiety about, or pain from the injection itself rather than the vaccine.
Examples: Syncope, local injection abscess, sciatic nerve damage (sciatica).
- **Coincidental:** Adverse event happens after immunization, but is not caused by the vaccine. It is a chance association, not directly related to vaccine.
Example: Diarrhea or pneumonia
- **Idiopathic or unknown:** The cause of the adverse event cannot be determined.

Box 10.3

Adverse events following immunization (AEFI) in relation to various vaccines

- **BCG:** Local erythema, pain, swelling. Infrequently, local accelerated reaction, axillary/cervical lymphadenitis (sometime suppurative) 2–6 month later. Rarely, osteitis, osteomyelitis, disseminated BCG infection 1 month–1 year later.
- **DTP:** Local soreness, induration, erythema. Infrequently, excessive/prolonged/inconsolable crying or screaming, irritability, loss of appetite, fever, HHE, shock, seizures, pseudotumor cerebri.
- **Measles/MMR:** Local erythema, pain and swelling. Infrequently, irritability, malaise and measles-like illness (mild). Rarely, febrile seizures, thrombocytopenia, anaphylaxis, toxic shock syndrome, encephalopathy.
- **OPV:** VAPP; extremely rare (1 per 2.5 million); more likely in more than 18 years of age and immunocompromised individuals; more with the first dose.
- **IPV:** Local erythema, soreness/pain, induration (only occasionally).
- **Hepatitis B:** Local erythema, pain, swelling. Infrequently, fatigue, GI upset, headache, myalgia, hypotension. Rarely, anaphylaxis.
- **Hepatitis A:** Local erythema, tender induration; infrequently, nausea, vomiting, anorexia, malaise, headache, fatigue, pyrexia.
- **Hib:** Local erythema, pain, swelling; Infrequently, fever, myalgia, hypersensitivity reactions.
- **Pneumococcal:** Local erythema, pain, induration; fever, myalgia.
- **Rotavirus:** Local pain and erythema; intussusception (rare, <1–2 in 100,000).
- **Varicella:** Local soreness, swelling, pain; rash (sometimes varicella-like). Infrequently, febrile seizures.
- **Meningococcal:** Local erythema, pain, swelling; pyrexia.
- **Japanese encephalitis:** Serious hypersensitivity reactions (transient), neurologic manifestations (encephalitis, encephalopathy).
- **Tetanus toxoid:** Local erythema, pain, swelling; malaise and other vague symptoms.
- **Yellow fever:** Local erythema, pain, swelling, headache, flu-like symptoms. Rarely, hypersensitivity reactions/anaphylaxis. Extremely rarely, vaccine-associated viscerotropic disease.
- **Flu:** Injectable (killed)–local reactions, oculorespiratory syndrome, GBS. Nasal spray (live attenuated)–wheeze, anaphylaxis.
- **Rabies:** Local pain, itching; headache, nausea, lymphadenopathy, myalgia. Rarely, GBS, serum sickness-like reaction, anaphylaxis.

Abbreviations: BCG, Bacillus Calmette–Guérin; DTP, diphtheria, pertussis and tetanus; HHE, hypotonia-hyporesponsive episode; OPV, oral polio vaccine; IPV, injectable polio vaccine; Hib, haemophilus influenzae type b; GBS, Guillain-Barre syndrome; VAPP, vaccine-associated paralytic polio; GI, gastrointestinal.

- An emergency kit should always be available at the time of administering the vaccine so that immediate remedial action is taken in case of an anaphylactic reaction.
- Never shake the reconstituted vaccine vial. Else, the virus clumping may occur. Rolling the vial containing lyophilized vaccine between palms assists in getting a clear, uniform solution.
- Following vaccination, the child should be observed for a minimum of 15 minutes.

SURVEILLANCE AND REPORTING

All AEFI are required to be reported to appropriate authorities for monitoring and surveillance.

VACCINE VIAL MONITOR

Vaccine vial monitor (VVM) is a thermochromic label put on vials containing vaccines (usually OPV) which gives a visual indication of whether the vaccine has been kept at a temperature which preserves its potency (Fig. 10.2). It was designed in response to the problem of delivering vaccines to resource-limited countries where the cold chain is difficult to preserve, and where vaccines are likely to be rendered inactive and administered ineffectively due to their having been denatured by exposure to ambient temperature.

If the small square within the circle matches the circle or becomes darker, the vaccine needs to be discarded even if its expiry date is still away.

ROUTE OF VACCINE ADMINISTRATION

- Sabin polio vaccine (OPV), typhoid Ty21 and cholera are the only vaccines given orally as of now.
- Live vaccines (measles, MMR) are best given subcutaneously (SC), in thigh of infants and deltoid area of older children.
- BCG is given intradermal (ID), usually over upper arm.
- Most vaccines (typhoid, diphtheria pertussis and tetanus {DPT}, hep B, HA, Hib) are given intramuscularly (IM), in infants over anterolateral aspect of thigh (in infants) and deltoid (in later age). It is advisable to

avoid the gluteal area because of risk of injury to sciatic nerve as also reduced immunogenicity of certain vaccines (Hep B and antirabies).

SAFE INJECTION PRACTICES

These should include:

- Separate syringe and needle for each injection.
- Separate anatomical sites and separate limb for multiple injections.
- Observation of the child for at least 15 minutes after administration of an injection for AEFI.
- Use of pre-injection preparation of the parent/child, distraction technique and a safe analgesic (paracetamol), if needed, for pain.

IMPORTANT GUIDELINES ON IMMUNIZATION (Principles of Immunization)

- The salient details, especially characteristics and anticipated adverse reaction(s) of the vaccine should be explained in simple terms to the parent(s) before its actual administration.
- Live vaccines must not be administered simultaneously with the exception of OPV and measles/MMR and OPV and oral typhoid vaccine (Ty21). At least four weeks gap should be kept between two live vaccines.
- As a rule, live vaccines are contraindicated in subjects with immunodeficiency, including immunosuppression from steroid or other such therapy. Only when a short course of low dose steroids is given for less than two weeks, these may be administered.
- Mixing of vaccines in one syringe is not permitted unless specified by the manufacturing company.
- Preparations for tackling adverse events should be in place before a vaccine is administered.
- The whole schedule need not be repeated in case of a delay or lapse in administering a particular vaccine.
- Minor illnesses such as upper respiratory infection (URI), diarrhea, slight fever, etc. are not contraindications to vaccination.
- Prematurity, protein energy malnutrition (PEM), antimicrobial therapy and minor allergy too are not valid contraindications to vaccination.
- As far as possible, combination vaccines, if available, should be preferred over individual vaccines to cut down visits as well as pricks.

RECOMMENDED IMMUNIZATION SCHEDULES IN INDIA

National Schedule

India's National immunization schedule is given in Table 10.5.

Indian Academy of Pediatrics Schedule

Indian Academy of Pediatrics—advisory committee on vaccines and immunization practises recommended (IAP-ACVIP) time-table and schedule is given in Table 10.6 and Fig 10.3.



Fig 10.2: Vaccine vial monitor (VVM). It ensures that the vaccines is potent when administered to the child.

Table 10.5: National immunization schedule

Beneficiaries	Age	Vaccine	No. of doses	Route of administration
Infants	6 weeks–9 months	DPT	3	Intramuscular
	6 weeks–9 months	Polio	3	Oral
	Birth–3 months	BCG	1	Intradermal
	9–12 months	Measles	1	Subcutaneous
Children	18–24 months	DPT	1*	Intramuscular
	18–24 months	Polio	1*	Oral
	5–6 years	DPT	1**	Intramuscular
	5–6 years	Typhoid	2	Subcutaneous
	10 years	TT	1**	Intramuscular
	10 years	Typhoid	1**	Subcutaneous
	16 years	TT	1**	Intramuscular
	16 years	Typhoid	1**	Subcutaneous
Vitamin A at 9 months, then every 6 months until 3 years (a total of only 5 doses – at 9, 15, 21, 28 and 36 months)				
Pregnant women	16–36 weeks	TT	1**	Intramuscular

* Booster doses

** 2 doses, if not vaccinated previously

Note: • Interval between two doses should not be less than one month.

• Minor coughs, colds and mild fever are not contraindications to vaccination.

• Pentavalent vaccine (DTP + Hib + Hep B) and inactivated polio vaccine (IPV) are being introduced in phased manner throughout India.

Abbreviations: DPT, diphtheria, pertussis and tetanus; BCG, Bacillus Calmette–Guérin; TT, tetanus toxoid.

Table 10.6: India's National Immunization Schedule (NIS)

Vaccine	When to give	Dose	Route	Site
For infants				
BCG	At birth or as early as possible till 1 year of age	0.1 mL	Intradermal	Left upper arm
Hepatitis B	At birth or as early as possible within 24 hours	0.5 mL	Intramuscular	Anterolateral side of mid thigh
OPV-0	At birth or as early as possible with first 15 days	2 drops	Oral	Oral
OPV-1, 2 and 3	At 6, 10 and 14 weeks	2 drops	Oral	Oral
IPV	At 14 weeks	0.5 mL	• Intramuscular • Subcutaneous	• Anterolateral side of mid thigh • Upper arm
DTP-1, 2 and 3	At 6, 10 and 14 weeks	0.5 mL	Intramuscular	Anterolateral side of mid thigh
Hepatitis B-1, 2 and 3	At 6, 10 and 14 weeks	0.5 mL	Intramuscular	Anterolateral side of mid thigh
Measles	9 completed months–12 months Give up to 5 years if not received at 9–12 months age)	0.5 mL	Subcutaneous	Right upper arm
Vitamin A (1st dose)	At 9 months with measles vaccine	1 lakh IU (1 mL)	Oral	Oral
For children				
DTP booster	16–24 months	0.5 mL	Intramuscular	Anterolateral side of mid thigh
OPV booster	16–24 months	2 drops	Oral	Oral
Measles (2nd dose)	16–24 months	0.5 mL	Subcutaneous	Right upper arm
Japanese encephalitis*	16–24 months with DTP/OPV booster	0.5 mL	Subcutaneous	Left upper arm
Vitamin A (2nd to 5th dose)	16, 22, 28, 36 months (every 6 months up to age of 3 years)	2 lakh IU (2 mL)	Oral	Oral
DTP booster	5–6 years	0.5 mL	Intramuscular	Anterolateral side of mid thigh
TT	10, 16 years	0.5 mL	Intramuscular	Upper arm
For pregnant women				
TT-1	Early in pregnancy (usually 16 weeks)	0.5 mL	Intramuscular	Upper arm
TT-2	4 weeks after TT-1**	0.5 mL	Intramuscular	Upper arm
TT-booster	If received 2 TT doses in a pregnancy within last 3 years	0.5 mL	Intramuscular	Upper arm

*In select states, districts and cities.

**Give TT-2 or Booster doses before 36 weeks of pregnancy.

However, give these even if more than 36 weeks have passed. Give TT to a woman even in labor if she has not previously received TT.

Note: (a) Interval between 2 doses of DPT, OPV and hepatitis B should not be less than one month.

(b) Minor cough, cold and mild fever are not a contraindication to vaccination.

(c) If the child has diarrhea, give a dose of OPV, but do not count this dose and ask the mother to return in 4 weeks for the missing dose.

(d) Pentavalent vaccine (DTP+Hep B+Hib) has been introduced NIS in several states.

Abbreviations: BCG, Bacillus Calmette–Guérin; OPV, oral polio vaccine; IPV, inactivated polio vaccine; DTP, diphtheria, tetanus, pertussis; TT, tetanus toxoid.

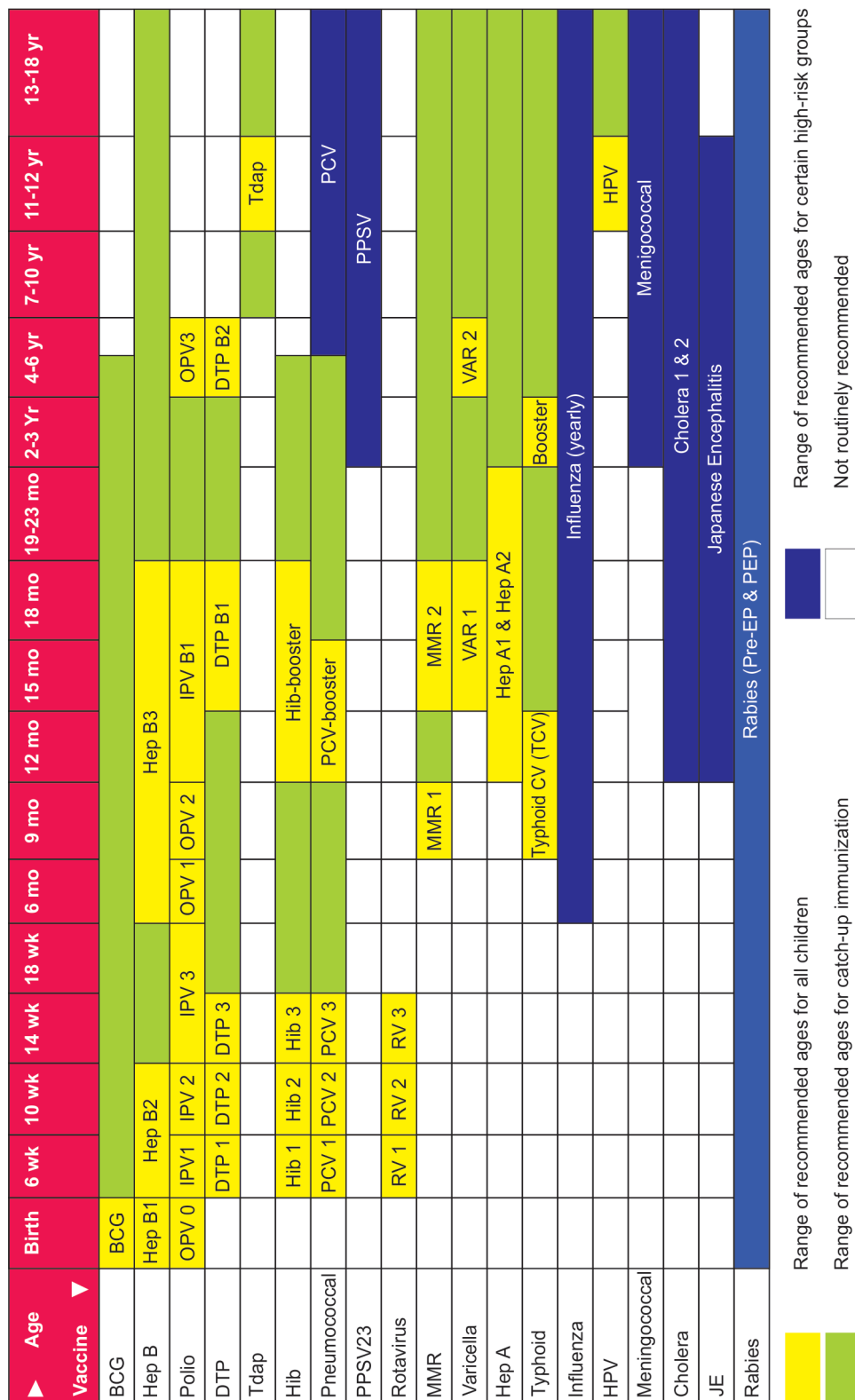


Fig. 10.3: Indian Academy of Pediatrics (IAP) immunization schedule.
Abbreviations: BCG, bacillus Calmette and Guérin; Hib, *Hemophilus influenza* type B; MMR, measles mumps and rubella; HPV, human papilloma virus; JE, Japanese encephalitis; PPSV, pneumococcal polysaccharide vaccine; OPV oral polio vaccine; Hep B, hepatitis B virus; Hep A hepatitis A virus; VAR, varicella; pr-EP, pre-exposure; PEP, post-exposure.

160 IMMUNIZATION OF ADOLESCENTS

IAP recommends two vaccines for adolescents whose basic earlier immunization is already complete, namely:

1. Tdap/Td at 10 years followed by Td every 10 years
2. Human papilloma virus (HPV) vaccine at 11–12 years; 3 doses only in girls till its approval is made for boys too.

Further details are available in Chapter 7 (Adolescent Medicine).

IMMUNIZATION OF THE IMMUNOCOMPROMISED

- Generally, all live vaccines are contraindicated in immunodeficiency (including steroid-induced immunosuppression with two mg/kg/day prednisolone; during or within three months of chemotherapy) in the wake of likelihood of disseminated disease by the attenuated pathogens in the vaccine.
- Killed (inactivated) vaccines and toxoids are permitted in such subjects, bearing in mind that their efficacy may be compromised. Hence additional doses may be required for optimal efficacy. At times, it may be advisable to even test for specific serum antibodies.
- Household contacts should be given inactivated polio vaccine instead of OPV to safeguard against the risk of transmission of live polio virus to the patient.
- In case of human immunodeficiency virus (HIV)
 - All vaccines can be given to asymptomatic subjects with the exception of BCG, OPV and yellow fever vaccines.
 - Symptomatic subjects should not be given live vaccines (BCG, measles, MMR, oral typhoid) with the exception when CD count is more than 15% for the age.
 - Infants born to HIV-positive mother, but with indeterminate HIV status should be vaccinated as normal infants.
 - Hepatitis B needs to be given in double the dose in for 4 doses for achieving acceptable seroconversion.
- In asplenia (functional or anatomical), including splenectomy: Pneumococcal (9 both conjugate and polysaccharide), Hib, meningococcal and typhoid vaccines should specially be given over and above routine vaccines.

IMMUNIZATION OF PRETERM/LOW BIRTH WEIGHT (LBW) INFANTS

Regardless of gestational age and birth weight, all vaccines can be given as per schedule according to the chronological age, except:

- In infants less than 2 kg, birth dose of hep B vaccine may be delayed till the age of one month in view of suboptimal immunogenicity. An alternative strategy is to give it at the time of discharge provided that weight gain has been satisfactory.
- Infants born to hep B-positive mothers and weight less than 2 kg should receive hepatitis immune globulin (HBIG) within 12 hours of birth and three more doses at 1, 2 and 6 months.

LAPSED IMMUNIZATION

In a child who has missed a certain vaccine(s), immunization should be given at the next visit as if the usual interval had elapsed, immunization should be completed at the next available opportunity. There is no need to restart afresh the vaccine series in question.

UNKNOWN IMMUNIZATION STATUS

A child with unknown immunization status should be considered **unimmunized**. He needs to be given immunization as in a child who is unimmunized.

BACILLUS OF CALMETTE AND GUÉRIN (BCG) VACCINATION

Bacillus of Calmette* and Guérin* (BCG) vaccine is an attenuated live vaccine obtained from the bovine strain of tubercle bacilli. It produces controlled primary tuberculosis infection. Thus, immunity to tuberculosis without exposure to risks of natural infection is accomplished. There is some evidence that BCG also protects against leprosy and leukemia.

The current practice is to employ heat stable, freeze-dried powder (to be reconstituted using normal saline) which should preferably be stored at 2–10°C. In India it is produced by the BCG laboratory, Guindy, Chennai. As recommended by the WHO, it is the Danish 1331 strain of the bacilli, available in multidose vials. More recently, isonix-resistant BCG vaccine has also become available. Once the BCG vial is opened, it has to be used within 4 hours. Leftover vaccine must be discarded.

AT WHAT AGE(S) TO VACCINATE?

In India, as in other developing countries, direct primary vaccination against tuberculosis is recommended at birth or earliest contact after birth.

SITE

The standard site is the middle of deltoid (just above its insertion) over the left upper arm. When BCG and triple vaccinations are being simultaneously given, it is advisable to choose different arms.

METHOD

0.1 mL of BCG is injected intradermally with a special tuberculin syringe. For mass immunization, the jet injector is of distinct value.

NORMAL REACTIONS FOLLOWING VACCINATION (IMMUNOGENICITY)

A papule appears in 2–3 weeks after vaccination. By about the fourth week, it grows in size to 4–8 mm. Then it either subsides or sheds into a shallow ulcer covered with a crust. This ulcer heals spontaneously in nearly 8–12 weeks' time,

* Two scientists of the Pasteur Institute, Paris, who developed this vaccine in early part of the 20th century.

leaving behind a tiny scar. After several years, this scar may fade and even entirely disappear.

There is, however, one noteworthy exception. If a tuberculin positive reactor is vaccinated, there is likely to be an accelerated response (Koch's phenomenon) with a papule or red angry ulcer at the injection site after only 1–3 days and lasting about 3 weeks. This is almost harmless and does not disfavor the present practice of direct BCG without prior tuberculin (Mantoux) test.

It seems to be appropriate to do Mantoux test 2–3 months after BCG administration. In case it turns out to be negative, BCG should be repeated.

CONTRAINDICATIONS

- Skin ailments like eczema and burns
- Immunodeficiency (hypogammaglobinemia, symptomatic HIV, deficient cell-mediated immunity)
- Immunosuppressant (e.g., steroid) therapy
- Within 4–6 weeks of immunosuppressive illnesses like measles
- Pregnancy.

AEFI AND THEIR MANAGEMENT

These are uncommon and rather mild:

- **Accelerated reaction** in tuberculous sensitive individuals.
- **Deep ulceration** of the vaccination site together with superadded bacterial infection.
- **Simple lymphadenitis** involving axillary lymph gland (less than 1 cm in diameter) without any progression or signs of suppuration should be regarded as a normal, though somewhat exaggerated, response to BCG and a part of the induced **primary complex**. It should be left as such.
- **Suppurative lymphadenitis**, axillary and/or cervical lymph glands, may attain considerable size (Fig. 10.4) and, at times, develop suppuration and abscess formation. This is termed **BCGosis** or **simply BCG adenitis**. Pyogenic antibiotics may be considered in such cases. Many surgeons, however, recommend excision of the glandular swelling. There is a good deal of consensus that every infant with BCGosis should have at least X-ray of the chest to exclude primary complex. The earlier practice of giving only isoniazid or isonicotinyl hydrazide (INH), 5–10 mg/kg/day, to every infant with BCG adenitis is no longer favored.
- **Keloid formation** over the site of vaccination.
- Infrequently, lymphadenitis (sometime suppurative) and accelerated BCG reaction.
- Very rarely, osteitis, suppurative osteomyelitis and disseminated tuberculosis (in immunocompromised states) may occur.

PROTECTIVE EFFICACY

BCG is expected to offer around 80% protection against serious forms of tuberculosis (miliary and central nervous



Fig. 10.4: BCGosis. Note the significant axillary lymphadenitis (persistent and progressive) following routine BCG vaccination. Eventually, it needed surgical excision.

system {CNS} tuberculosis), about 50% protection against pulmonary tuberculosis and no protection against simple tuberculous infection.

POLIO VACCINATION

Oral polio vaccine (OPV), Sabin vaccine, is a live, but attenuated virus (Fig. 10.5). Storage is best done at 2–10°C. Since it is cheaper, easy to administer, helps to prevent establishment and spread of wild pathogenic poliovirus in the community, and can be used in blanketing operations to check the spread of an incipient outbreak, it is being used by a large majority of the countries the world over. This has earned it the designation of **community vaccine**.

The killed (inactivated) injectable polio vaccine (IPV), the so-called **Salk vaccine***, is required to be administered



Fig. 10.5: Oral polio vaccine (OPV). OPV has played a major role in near eradication of poliomyelitis.

* After the name of Dr Jonas Salk (1914–1995) who discovered the ground-breaking inactivated polio vaccine. He was awarded the “1976 Nehru Award for International Understanding” at a special ceremony held at the All India Institute of Medical Sciences (AIIMS), New Delhi, India.

Table 10.7: Salk vs Sabin vaccine

Salk vaccine	Sabin vaccine
Killed and formalized	Live attenuated
Expensive	Relatively cheap
Administered parenterally (intramuscular or subcutaneous injection)	Administered orally, hence easy and less cumbersome for patient as well as the worker
Immunity shortlived	Quite prolonged
Does not produce local intestinal immunity since antibodies are in the circulation	Produces both local as well as circulation (general) immunity
Reinfection with wild poliovirus possible though it does prevent paralysis	Reinfection with wild poliovirus as well as paralysis are prevented
Offers no protection to the non-vaccinated people	Through cross infection, others are also protected
Of no significant value in controlling epidemics of poliomyelitis	Of definite value

parenterally. It does not interfere with the spread of natural virus in the community though it does produce individual immunity to polio. The differences between the Salk and Sabin vaccines are highlighted in Table 10.7.

ORAL POLIO VACCINE (OPV)

Availability

It is available as a trivalent antigen providing three strains of poliovirus (Lansing, Leon and Brunhilde). Monovalent OPV (mOPV) providing only one strain, is also available.

Dosage Schedule

- **National:** Primary doses are given at birth (birth/zero dose), then at 6 weeks, 10 weeks, and 14 weeks. A booster dose is given in second year (15–18 months) and yet another in the fifth year. A total of 6 doses are, therefore, recommended to ensure reasonably high personal protection from poliomyelitis.
- **IAP-ACVIP:** Now that India is polio-free, IAP-ACVIP has adopted the **sequential IPV-OPV** schedule in run-up to **all IPV** schedule in due course of time.
- **Recommended schedule:** Birth dose of OPV, three primary doses of IPV at 6, 10 and 14 weeks followed by two doses of OPV at 6 and 9 months, another booster dose of IPV at 14–18 months, and OPV at 5 years. Additionally, OPV should be given on all supplementary immunization activities (SIAs). Catch-up is till 5 years of age.

OPV given in pulse polio immunization (PPI), i.e. on National Immunization Day (NID) and Subnational Immunization Day (SNID) campaigns should be considered over and above these doses. OPV requires to be essentially administered even if the child has suffered from the disease.

In grown-up children (beyond 8 years of age) polio vaccine may not be given. This is because the older children are more or less immune to natural infection with poliovirus.

Administration

OPV is administered as two drops (providing serotype 1, 2 and 3) directly into the mouth. This should be followed with the feeding of some water to ensure absolute ingestion of the vaccine. It is now convincingly shown that antibodies in breast milk against poliomyelitis do not interfere with the take of the vaccine and the consequent immune response. Breastfeeding need not be skipped before and after OPV administration.

Pulse polio means simultaneous mass immunization of all infants and children under 5 years at a particular date, i.e. NID during winter (usually December-January) regardless of their immunization status. It is over and above the routine doses of OPV.

It is thanks to the very aggressive pulse polio campaign, including **mopping-up** and **ring immunization** spread over almost two decades that India has succeeded in being polio free.

Mopping-up means administration of OPV, in two doses 4–6 week apart, to all children under 5 years regardless of their immunization status in areas at high-risk for transmission of wild polio virus. For this purpose, house-to-house visits are made in the concerned area.

Ring immunization means administration of OPV, in two doses 4–6 week apart, to all children under 5 years within an area of 5 km within 48 hours of finding a case of polio. For “pulse immunization”, See Chapter 12 (Infant and Young Child Feeding).

How OPV Behaves in the Body?

On entry in the gut, strains of OPV multiply. As a result there is production of local as well as systemic immunity. The vaccine also leads to production of antibodies like IgG, IgM and IgA. The last-named is said to contribute to the local immunity whereas the remaining two limit spread of the poliovirus to the CNS and protect against paralysis.

Contraindications

- Severe diarrhea and an acute illness
- Leukemia and other malignancies
- HIV (immunocompromised state and symptomatic).

AEFI

Though OPV is exceedingly safe, it may cause:

- Mild diarrhea in case of overdose
- Vaccine-associated paralytic poliomyelitis (VAPP) due to vaccine virus per se very rarely (one in 2.5 millions).

Vaccine Vial Monitoring

If the inner square of the vial matches the outer square or becomes darker, the vaccine should be discarded.

INACTIVATED POLIO VACCINE (SALK VACCINE)

With the eradication of polio, eventually OPV has got to give way to IPV. A policy decision for the National immunization program is awaited. However, IAP has already recom-

mended in office practice the sequential OPV-IAP schedule which is to be followed in due course by all IPV schedule.

- **Dosage schedule:** 0.5 mL (SC) in lateral thigh in infants and deltoid in grown-up children at 6, 10 and 14 weeks. Booster is required at 14–18 months. Additionally, OPV is also given—at birth, 6 months, 9 months and 5 years.
- **AEFI:** No significant side-effects.
- **Storage:** 2–8°C.
- **Availability:** As such and in combination with other vaccines.

HEPATITIS B VACCINE

Hepatitis B vaccine consists of hepatitis surface antigen related protein—a highly purified suspension of inactivated, alum-adsorbed hep B surface antigen (HBsAg) particles. Now only deoxy ribonucleic acid (DNA) recombinant, i.e. genetically engineered (Engerix-B, Shanvac-B, hep B Vac, Enivac HB, Revac-B) vaccine is in vogue worldwide. The WHO recommends incorporation of the hep B vaccine as the seventh vaccine in the routine immunization schedule in the South-East Asia and the Pacific.

INDICATIONS

It is now recommended as a routine vaccine. High-risk situation in which it must be given include:

- Recipients of multiple blood transfusions
- Household sexual contacts of carriers of hep B virus
- Users of parenteral drugs such as heroin
- Hemosexually active males
- Hemodialysis subjects
- Immigrants from areas of high hep B virus endemicity
- Babies born to mothers with HBsAg positive blood.

DOSE

The vaccine is administered intramuscularly in a dose of 0.5 mL (10 µg) and 1 mL (20 µg) for children below and above 10 years, respectively.

DOSAGE SCHEDULE

- **National:** At birth within 12 hours of delivery, 6 and 14 weeks.
- **IAP-ACVIP:** At birth, 6 weeks, 6 months (0–6 weeks–6 months); birth, 6 and 14 weeks, or birth, 6, 10 and 14 weeks. Else, it may be given in two doses one month apart followed by a booster 6 months later.
- **Post-exposure prophylaxis:** According to IAP recommendation, if the pregnant woman is a known carrier of hep B virus, her neonate should be given hep B immune globulin (HBIG) within 12 hours of birth and also one dose of hep B vaccine with a separate syringe and needle over a different site on the body. If HBIG is not available, hep B vaccine must be given. If there has been a delay of over 12 hours, HBIG need not be given. However, hep B vaccine has got to be started. The second dose of the vaccine is given 4 weeks later and the third 5 weeks (4–6 weeks) later. It may well be convenient to give the third dose at the same time as measles vaccine, at or after 9 months.

In case the mother is known not to be a carrier of hep B, there is no need to give hep B vaccine immediately after birth. It can conveniently be given at the first visit for other vaccines, such as 6 weeks when a dose of DPT or OPV is due. The second dose of hep B vaccine may be given 4 weeks later and the third at the time of measles vaccine.

AEFI

- Transient soreness, erythema and induration at injection site
- Low grade fever.

There is no evidence that it causes development or flare-up of demyelinating diseases such as multiple sclerosis (suspected in France a few years ago).

CONTRAINDICATION

Hypersensitivity to its components.

STORAGE

2–8°C.

DIPHTHERIA, TETANUS AND PERTUSSIS (DTP) VACCINATION

DTP (triple) vaccine offers combined prophylaxis against diphtheria, pertussis and tetanus. The pertussis toxoid offers administrative convenience as well as potentiates the effect of diphtheria toxoid.

Both whole cell (DTwP) and acellular (DTaP) vaccines are available. The latter is safer and also available as reduced antigen Tdap booster vaccine for use in older children more than 7 years and adolescents in whom immunity against DTP may have waned.

DOSAGE SCHEDULE

- **National:** Primary vaccination consists in giving three doses at the age of 6, 10 and 14 weeks followed by booster at 15–18 months and 5 years.
- **IAP-ACVIP:** Primary vaccination consists in giving three doses at the age of 6, 10 and 14 weeks followed by booster at 15–18 months, and 5 years. For boosters, acellular vaccine (DTaP) may be used to safeguard from higher reactogenicity. DTaP may be preferred over DTwP in children severe AEFI to previous dose of DTwP or children with neurologic disorders.

ADMINISTRATION

A dose of 0.25–0.5 mL, deep intramuscularly over the anterolateral aspect of thigh or the deltoid. Local painful swelling, infrequently even sterile injection abscess may occur.

AEFI

- Fever (within 48 hours)
- Febrile seizures (within 72 hours)
- Inconsolable, persistent crying >3 hours (within 48 hours of injection)

- 164** ■ Transient hypotonia-hyporesponse episode (within 48 hours)
- **Collapse**—occasionally 1–3 hours after injection, development of pallor, sweating, slow pulse from which the child invariably recovers in an hour or two
 - Allergic skin rash
 - Pseudotumor cerebri
 - Encephalitis.

CONTRAINDICATIONS

The only contraindications to DTP immunization are:

- Progressive neurologic diseases.
- Severe anaphylactic reaction to previous DTP injection.
- Encephalopathy within 7 days of previous DTP injection.

STORAGE

2–8°C.

HEMOPHILUS INFLUENZAE TYPE B VACCINE

This vaccine (Hiberix, HIBest, ACT-HIB, Hib Titer) aims at protecting against *H. influenzae* type B infection (pneumonia, epiglottitis, meningitis) which is believed to cause significant morbidity and mortality in infants and toddlers.

At least four conjugate polysaccharide Hib vaccines are available, namely:

1. Diphtheria toxoid conjugated vaccine (PRP-D),
2. Oligosaccharide conjugated vaccine (HbOC),
3. Meningococcal OMP conjugate vaccine,
4. Tetanus toxoid conjugated vaccine (HiB-TT, PRP-T).

INDICATIONS

As a routine vaccine for protection against *Hemophilus influenzae* type B, usually simultaneously with DPT. High-risk situations where it must be given even in older children include:

- Immunodeficiency disorder
- Asplenemia (both anatomical and functional) including sickle-cell anemia
- Lymphoblastic leukemia
- Hodgkin lymphoma.

DOSE

0.5 mL IM over anterolateral aspect of thigh or deltoid.

DOSAGE SCHEDULE

- **National:** The vaccine is administered in three doses, at 6, 10 and 14 weeks. Booster is recommended at 15–18 months. If a child first reports between 6 and 12 months, only two primary injections and more than one year, only one injection is recommended.
- **IAP-ACVIP:** Primary series at 6, 10 and 14 weeks; booster at age 12 through 18 months.

AEFI

Hib vaccine is very safe, usually causing no local or systemic reaction. It does not increase the risk of insulin-dependent diabetes mellitus (IDDM) due to formation of islet-cell antibodies as suggested earlier.

CONTRAINDICATION

Hypersensitivity to its components.

STORAGE

2–8°C.

PNEUMOCOCCAL CONJUGATE VACCINE

AVAILABILITY

As pneumococcal conjugate vaccine (PCV) 10 and PCV 13.

DOSE

0.5 mL SC or IM over anterolateral aspect of thigh.

DOSAGE SCHEDULE

- **National:** Not yet incorporated
- **IAP-ACVIP:** Primary at 6, 10 and 14 weeks; booster at 12–15 months.

AEFI

- Local soreness and pain
- Fever
- Malaise.

CONTRAINDICATION

Anaphylaxis after previous dose.

STORAGE

2–8°C.

PNEUMOCOCCAL POLYSACCHARIDE VACCINE (PPSV)

The polyvalent pneumococcal vaccine claims to protect against most of the commonly encountered pneumococcal infections like pneumonia, bacteremia, meningitis and otitis media.

INDICATIONS

It is indicated in only high risk children and for routine use in healthy children.

- Chronic diseases, e.g. cardiac, pulmonary, renal or metabolic disease.
- Anatomical or functional asplenemia.
- Immunocompromised children—HIV, nephritic syndrome, immunosuppressant therapy, organ transplantation, congenital immunodeficiency.

DOSE

0.5 mL (IM, SC).

DOSAGE SCHEDULE

- At two years of age or later, ensuring an interval of at least eight week after the last dose of PCV.
- Revaccination after five years until age of 10 years.

AEFI

These include local painful swelling, pyrexia, Guillain-Barre syndrome, relapse of disease in immune thrombocytopenic purpura (ITP) and anaphylaxis.

ROTAVIRUS VACCINE

Three oral rotavirus vaccines are:

1. **Human monovalent live vaccine (RV₁) (Rotarix GSK):** Live attenuated vaccine providing the human rotavirus GIP(8).
2. **Human bovine pentavalent live vaccine (RV₅) (Rota-Teq):** Live attenuated vaccine providing rotavirus strains reassorted between the bovine and human WC3 rotaviruses.
3. **Indian neonatal rotavirus live vaccine, 116E:** The Indian rota vaccine is yet to be licensed.

INDICATIONS

For safeguard against severe rotavirus diarrhea.

DOSE

- **RV₁ (Rotarix):** Two doses, each one mL (lyophilized) or 1.5 mL (liquid)
- **RV₂ (Rota Teq):** Three doses, each two mL (liquid).

DOSAGE SCHEDULE

- **National:** Not yet included
- **IAP-ACVIP:**
 - RV₁—2 doses 4 weeks apart at 6 and 10 weeks or 10 and 14 weeks age.
 - RV₂—3 doses 4 weeks apart – 6, 10 and 14 weeks.

Initiation of each vaccine should be before end of 14 week, the last dose given before 32 weeks.

AEFI

A safe vaccine. Rarely, intussusception.

CONTRAINDICATIONS

- Severe immunodeficiency state
- Previous h/o intussusception.

PRECAUTIONS

- Avoid during an acute attack of gastroenteritis/diarrhea or some other illness
- Protect from exposure to light
- Once it is reconstituted/vial is opened, it should be immediately administered.

STORAGE

2–8°C.

MEASLES VACCINATION

A live, attenuated measles vaccine (Schwartz strain from chick embryo tissue culture, Edmonston strain from human diploid cells), has a definite protective value of as high a

magnitude as 95–100%. A single dose produces antibodies for an indefinitely prolonged period. Boosters are usually not needed.

An aerosol measles vaccine has yielded gratifying results in Mexico. Besides convenience in administration, it may well overcome other limitations of the injection.

DOSE

0.5–1.0 mL (SC, IM) preferably over the upper arm/anterolateral aspect of thigh.

DOSAGE SCHEDULE

- **National:** At 9–12 months of age with revaccination at 15–18 months in the form of MMR vaccine. In high-risk situations it may be given earlier, but in that event, it must be repeated after a gap of 6 months.
- **IAP-ACVIP:** At 9 months or 270 complete days as MMR followed by MMR at 12 through 18 months and 4 through 6 years.

AEFI

Practically no remarkable complications occur if the vaccine is administered carefully and precautions taken in the wake of the relative contraindications.

- Mild measles-like illness with fever and rash 5–10 days after immunization
- Febrile reactions for a day or two from fifth to twelfth post-vaccination day in a proportion of the cases
- Febrile seizures
- Slight gastrointestinal upset
- Rhinopharyngitis
- Toxic shock syndrome.

CONTRAINDICATIONS

- Acute illness
- Immunosuppressive therapy (steroids, antimetabolites, alkylating agents) over prolonged period
- History of convulsions in the child or the family
- Leukemia
- Active tuberculosis
- Immune deficiency states (hypogammaglobulinemia, severe HIV)
- Recent gammaglobulin administration
- Allergy/eczema.

PRECAUTION

Reconstituted vaccine must be protected from light, employed the same day (within 4–6 hours after reconstitution) and the leftover discarded.

STORAGE

2–8°C.

RUBELLA VACCINATION

Rubella vaccine too is a live attenuated vaccine. Rubella vaccination decidedly protects against the occurrence of so-called **congenital rubella syndrome** in the offspring.

166 INDICATIONS

- Immunization of girls from one year to puberty
- Susceptible women of child-bearing age (with hemagglutination test negative) provided they are not already pregnant and conception is unlikely in the subsequent 3 months.

DOSE

0.5 mL (SC) upper arm as a single dose.

CONTRAINDICATION

- Febrile respiratory illness
- Pregnancy.

AEFI

Local pain, erythema and induration at injection site.

MEASLES, MUMPS AND RUBELLA (MMR) VACCINE

MMR, a live attenuated vaccine (Priorix) providing protection against measles, mumps and rubella.

INDICATION

As a backup dose for protection against measles in the second year of life (at around 15 months of age, at least 3 months following primary measles vaccination in the first year) and 4–6 years, as also for protection against mumps and rubella.

DOSE

0.5 mL (SC) at anterolateral aspect of thigh or deltoid.

DOSAGE SCHEDULE

- **National:** At 15 months
- **IAP-ACVIP:** First dose at 9 months followed by a booster at 12–18 months and the second booster at 4 through 6 months later, up to 5 years of age.

AEFI

- Fever
- Febrile seizures
- Lymphadenitis
- Parotitis.

The suspicion of a causal relationship of MMR vaccine with autism is unfounded.

VARICELLA VIRUS (CHICKENPOX) VACCINE

A live attenuated varicella virus vaccine (Varilrix, Okavax) provides a high degree of protection against chickenpox. It is quite expensive.

INDICATION

Active immunization against chickenpox after 1 year of age.

DOSE

0.5 mL SC.

DOSAGE SCHEDULE

- **National:** Not yet included
- **IAP-ACVIP:** Primary dose at 15–18 months followed by a second dose at 4 through 6 years of age.

AEFI

Both the vaccines are quite safe and well tolerated. Locally, a mild transient reaction may occur. Rarely, rash may be encountered.

CONTRAINDICATIONS

- Acute severe febrile illness
- Immunodeficiency, especially, HIV subjects with lymphopenia, i.e. total leukocyte count (TLC) <1200/mm³
- Recent administration of immunoglobulins
- Known anaphylaxis—egg allergy, neomycin hypersensitivity.

PROTECTION

In children exposed to chickenpox case, efficacy is 80% in protecting against chickenpox provided that it is administered within 3 days of exposure to a case of chickenpox.

HEPATITIS A VACCINE

INDICATION

Active immunization against hepatitis A, especially in children who are less likely to have developed natural immunity because of a sophisticated lifestyle.

DOSE

720 units from 1 year to (and including) 18 years, and 1440 units from 19 years onward.

DOSAGE SCHEDULE

- **National:** Not yet included
- **IAP-ACVIP:**
 - **Killed vaccine (Havrix):** It is given IM over anterolateral aspect of thigh or deltoid in two doses 6–18 months apart.
 - **Live attenuated (Biovac):** Same two doses regimen.

AEFI

- Transient painful injection site
- Nausea, vomiting, headache, malaise, anorexia
- Fever.

STORAGE

2–8°C.

TYPHOID VACCINATION

Currently recommended vaccines are:

- Injectable Vi capsular polysaccharide typhoid vaccine (Typhim Vi, Vac Typh, Typhivax, Typho-Vi, Tyvax-Vi).
- Conjugate typhoid vaccine
- Oral typhoid vaccine-Ty21.

Whole-cell killed TA vaccine (as it also includes *Salmonella paratyphi A*), though quite cheap and effective, is no longer manufactured locally in India.

TYPHOID Vi POLYSACCHARIDE VACCINE

It contains purified Vi capsular polysaccharide (ViCPS). The dose is one injection (0.5 mL containing 25 µg of ViCP9) given SC or IM as a single dose every 3 years. It confers a protection of 75–100%. Only mild local pain and fever may rarely occur as side-effects. Contraindications include hypersensitivity and pregnancy. Ideally, for maximal protection, these vaccines are recommended to be administered after 5–6 years of age.

Dose/Schedule

- **National:** Not yet included
- **IAP-ACVIP:** 0.5 mL each (SC, IM) over anterolateral aspect of thigh at more than 2 years of age. Repeat every 3 years.

AEFI

- Local pain and induration
 - Fever and body pains over the next 2–3 days.
- Reactogenicity is less in monovalent (containing endotoxin of *Salmonella typhi* only) vaccine, acetone killed and dried preparation (AKD vaccine).

Contraindication

Anaphylactic reaction after the previous dose.

Storage

2–8°C.

Vi POLYSACCHARIDE CONJUGATE TYPHOID VACCINE

Two brands are available: Typhobar-TCV and PedaTyph

Dose/Schedule

- **National:** Not yet included
- **IAP-ACVIP:** Primary dose at 9–12 months. Booster in second year. At present only Typhobar-TCV stands recommended.

AEFI

Local pain and induration, pyrexias.

Contraindication

Anaphylactic reaction after the previous dose.

Storage

2–8°C.

ORAL TYPHOID VACCINE: TY21

It contains Ty21 live attenuated mutant strains of *Salmonella typhosa*. It confers a protection varying from 67–95%. For quite a few years, it is not available in India.

Dose

One capsule on day 1, 3 and 5 one hour before a meal, given every 3 years in children more than 6 years.

AEFI

The vaccine is well tolerated. Rarely slight gastrointestinal upset and rash may occur.

Contraindications

Immunodeficiency, immunosuppressant drugs, antimitotics, certain antibiotics and sulfas active against *salmonella*, acute febrile illness, gastrointestinal tract infection, and pregnancy.

Caution

Protection from light is vital for its stability.

Storage

2–8 °C.

HUMAN PAPILLOMA VIRUS (HPV) VACCINE

It is also called **anti cervical cancer vaccine**, HPV vaccine is of two types:

1. Bivalent vaccine (HPV2) (Cervarix)
2. Quadrivalent vaccine (HPV4) (Gardasil).

INDICATIONS

Protection against HPV infection and subsequently cervical cancer.

DOSE

0.5 mL IM over deltoid.

DOSAGE SCHEDULE

- **National:** Not yet included
- **IAP-ACVIP:** All females aged 11 or 12 years should be given any of the two vaccines.
 1. **Cervarix:** 0, 1 and 6 months
 2. **Gardasil:** 0, 2, and 6 months

AEFI

- Local erythema and painful swelling
- Fever.

CONTRAINDICATIONS

- Anaphylactic reaction to the previous dose
- Pregnancy.

168 PRECAUTION

Protect from exposure to light.

STORAGE

2–8°C.

INFLUENZA VACCINE

Influenza (flu) vaccine is now available in India under the trade names Vaxigrip (Sanofi-Pasteur) and Fluarix (GSK). This vaccine (A and B) prepared from currently prevalent strains is a trivalent inactivated vaccine (killed), giving a reasonable degree of protection for a short time only.

INDICATIONS

In India it is recommended for certain high risk conditions:

- Chronic cardiac, pulmonary (excluding asthma), hematologic and renal conditions (including nephrotic syndrome), chronic liver disease, and diabetes mellitus.
- Chronic and acquired immunodeficiency (including HIV infection)
- Laboratory personnel and healthcare workers.

DOSE/SCHEDULE

- **National:** Not yet included
- **IAP-ACVIP:**
 - **6 months–9 years:** Two doses of 0.25 mL (SC, IM) 1 month apart.
 - **More than 9 years:** 0.5 mL (SC, IM) as a single dose. Revaccination is needed every year using a single dose.

AEFI

- Local pain, induration and erythema
- Anaphylaxis
- Allergic reactions to components of vaccine.

CONTRAINDICATION

Hypersensitivity to its components.

STORAGE

2–8°C.

MENINGOCOCCAL VACCINE

Meningococcal vaccine is of two types:

1. Unconjugated polysaccharide vaccine
2. Conjugated group C vaccine.

INDICATIONS

- All residents of an epidemic area
- Close population groups, say schools
- All contacts of an index case, especially family members (in addition to the drug prophylaxis)
- High-risk groups—asplenia and immune (complement) deficiency
- Before travel to high endemic countries.

DOSE/SCHEDULE

- **Under 2 years:** 0.5 mL (deep SC), preferably in deep infraspinal fossa, in a single dose.
- **Over 2 years:** Two injections at 3–5 year gap, if required.

AEFI

- Local redness and edema
- Pyrexia.

CONTRAINDICATION

Anaphylactic reaction to a previous dose.

STORAGE

2–8°C.

JAPANESE ENCEPHALITIS VACCINE

Japanese encephalitis (JE) vaccine is the single most important control measure against Japanese encephalitis. Three types of new generation JE vaccines are licensed in India, namely—

1. Live-attenuated cell culture-derived SA-14-14-2
2. Inactivated JE vaccine Vero-cell culture-derived SA 14-14-2 (JEEV-BE)
3. Vero cell culture-derived, 821564XY, JE vaccine (JENVAC – Bharat Biotech).

INDICATION

Individuals living in the rural areas of JE endemic districts.

DOSE/SCHEDULE**Live Attenuated Culture-Derived SA-14-14-2**

- Minimum age—8 months
- Two dose schedule, first dose at 9 months along with measles vaccine and second at 16–18 months along with DTP booster
- Not available in private market for office use.

Inactivated Cell Culture-derived SA-14-14-2 (JEEV by BE India)

- **Minimum age:** 1 year (US-FDA: 2 months)
- **Primary immunization schedule:**
 - Two doses of 0.25 mL each administered intramuscularly on day 0 and 28 for children aged more than 1–3 years.
 - Two doses of 0.5 mL for children more than 3 years adults more than 18 years.

Inactivated Vero cell culture-derived Kolar strain, 821564XY, JE vaccine (JENVAC by Bharat Biotech)

- **Minimum age:** 1 year
- **Primary immunization schedule:** Two doses of 0.5 mL each administered intramuscularly at 4 weeks interval
- Need of booster still undetermined.

AEFI

JE vaccine is quite safe.

CONTRAINDICATION

JE vaccine is contraindicated in high fever, diabetes mellitus, liver and heart disease and immunodeficiency.

ORAL CHOLERA VACCINE

A special category vaccine, not required by healthy subjects in nonendemic areas. This new whole cell oral vaccine is now considered the best.

INDICATIONS

Individuals residing in highly endemic areas and travelling to areas where risk of transmission is very high, i.e. huge congregations as in Kumbh mela, natural calamities/disasters.

DOSE/SCHEDULE

IAP-ACVIP: Hol-TM which is manufactured and licensed in India. Two oral doses 2 weeks apart in subjects more than one year of age.

AEFI

Quite safe.

STORAGE

2–8°C. Shelf-life at this temperature range is 2 years.

YELLOW FEVER VACCINE

This is a live-attenuated vaccine against yellow fever (YF) which is prevalent in Sub-Saharan Africa, Central and South America. It is available as a single/multi-dose vials.

INDICATION

Those travelling to sub-Saharan Africa and some tropical South American countries.

DOSE/SCHEDULE

0.5 mL SC, IM over anterolateral aspect of thigh or lateral aspect of upper arm as a single dose which confers life-long immunity. Minimal recommended age is 9 months.

AEFI

- **Mild:** Fever (low grade), headache and myalgia
- **Severe (rare):**
 - **Immediate**-Hypersensitivity reaction (rash, urticaria, bronchospasm, etc) anaphylactic reactions.
 - **Later-YF vaccine-associated neurologic disease (YEL-AND):** Meningoencephalitis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, bulbar palsy, Bell palsy
 - **YF-vaccine-associated viscerotropic disease (YEL-AVD):** Multisystem organ failure.

CONTRAINDICATIONS

Age less than 6 months, allergy to vaccine component(s), primary immunodeficiency, immunosuppressive or immunomodulatory therapies, symptomatic HIV or CD4 T-lymphocytes <200 mm³ (or 15% of total in <6 years), thymus disorders associated with abnormal immune-cell function, malignant neoplasm and organ transplantation.

PRECAUTIONS

Avoid in infants aged 6–8 months, asymptomatic HIV, pregnancy and breastfeeding.

STORAGE

2–8°C (must not be frozen).

VACCINATION AGAINST RABIES

The categories of rabies exposure and recommended post-exposure prophylaxis are given in Table 10.8.

The old, conventional vaccine, an inactivated (by treatment with an agent called betapropiolactone) suspension of sheep brain, carries high risk of neurologic reactions (meningoencephalitis, ascending paralysis, polyneuritis). There is no justification for using it in the wake of availability of the following two modern tissue culture vaccines (MTC) which are potent and safe.

- **Human diploid cells (HDC) vaccine** is a sure, safe and painless preventive measure against hydrophobia. It is a lyophilized, stabilized suspension of rabies virus completely inactivated by β -prolactone. It is prepared on the human deployed cells.

This vaccine is given as 1 mL subcutaneous injections immediately after exposure, on 3rd day, 7th day, 14th day, 30th day and 90th day (last one optional). In case antirabies treatment is begun immediately with cleansing of the bitten area with soap and water and administration of antirabies serum (human or animal) sixth injection may well be missed.

Table 10.8: Categories of rabies exposure and need for post-exposure prophylaxis

Category of bite	Nature of contact	Exposure type	Post-exposure prophylaxis needed
I	Touching, feeding, lick on intact skin	None	None
II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding	Minor	Wound management + antirabies vaccine
III	Single or multiple transdermal bites or scratches, licks on broken skin; contamination of mucous membrane with saliva (licks)	Severe	Wound management + rabies immunoglobulin + antirabies vaccine

170 HDC rabies vaccine, unlike the conventional antirabies vaccine, is very safe. In 1%, redness and induration at the injection site may occur. Slight pyrexia and asthenia occur with the same frequency.

- **Purified chick embryo cell (PCEC)** is next to HDC in potency. It is now being locally manufactured in India at Ankleshwar, Gujarat, and is available under the proprietary name Rabipur (Hoechst). Its administration is in the same schedule as for HDC vaccine.

SEROPROPHYLAXIS

Seroprophylaxis with rabies human immunoglobulin (RHIG), 20 IU/kg, or rabies animal immunoserum, 40 IU/kg, as a single injection is recommended in all cases with severe exposure (category III) bites. It should be given as soon as possible preferably immediately after the bite. After 7–8 days of bite, it is unlikely to be of any benefit. Half of the dose is infiltrated in the tissues around the bite and the remaining half injected intramuscularly.

PRE-EXPOSURE PROPHYLAXIS

It is by a modern tissue culture vaccines (MTCV) on days 0, 7 and 28 intramuscularly.

COMBINATION VACCINES

(Comb Vaccines)

BACKGROUND

Two fundamental issues that resulted in development of combination vaccines are:

1. Modern recommendations comprising of 20 vaccines in the very first year of life necessitate far too many pricks and visits to the facility, thereby causing difficulties for the parents and avoidable pressure on the facility.
2. An infant's immune system is capable of responding to several antigens introduced simultaneously through a single prick in an effective way.

DEFINITION

A combination vaccine is defined as a vaccine that aims at providing protection against a number of infectious diseases through more than one antigen (immunogen) in a single preparation.

In other words, such a vaccine contains several immunogens in a single shot for protection against quite a few infectious diseases. The immunogens (antigens, even serotypes) may belong to different pathogens (e.g. DTP, MMR) or same pathogen (e.g. trivalent polio vaccine, trivalent influenza vaccine {TIV}). Understandably, its efficacy, immunogenicity and safety profile is comparable to the singly administered vaccines.

The commonly held understanding about the term, combination vaccines, is for vaccines containing multiple pathogens, e.g. DTP (both DT_wP and DT_aP), MMR, DT_wP + Hib, DT_aP + Hib, DT_wP + Hep B, etc. However, single pathogen vaccines with different antigen belonging to the same pathogen like OPV, IPV, influenza, pneumococcal, etc. are also combination vaccines since they contain various antigens or serotypes of a pathogens.

BENEFITS

The earliest combination vaccine to become available was DPT/DTP in 1945 followed by MMR in 1971. Various tetravalent and pentavalent vaccines are built up around DTP.

CONSUMER-RELATED BENEFITS

- Reduction in number of pricks
- Reduction in number of visits to the health center
- Reduction in cost of administering and stocking vaccines
- Improved compliance, resulting in fall in incidence of missed vaccinations
- Facilitation in the introduction of new vaccines in the immunization schedule.

HEALTH DEPARTMENT/FACILITY-RELATED BENEFITS

- Reduction in pressure on cold chain
- Reduction in paper work
- Enhanced compliance, contributing to success of immunization program
- Reduced vaccination visits
- Economic gains—reduced expenditure on packaging, transportation, cold chain maintenance, infrastructure, manpower, etc.

ADVERSE EFFECTS

A marginal increase in incidence of minor AEFI may occur following a combination vaccine. AEFI, if any, are on similar lines as in case of singly administered vaccines though with somewhat higher frequency than in case of the latter. Adverse effects include febrile seizures. The risk of seizures is higher on the day of vaccination.

BENEFITS VIS-À-VIS ADVERSE EFFECTS

All in all, compared to an increase in AEFI, advantages of combination vaccines are overwhelming, outweighing the slight hike in adverse events, and justifying their enhanced use.

RECOMMENDED COMBINATION VACCINES

Table 10.9 lists the recommended combination vaccines.

Table 10.9: Combination vaccines available**Currently licensed combination vaccines in India****Antigens of same pathogen****• Pneumococcal**

- Pneumococcal polysaccharide vaccine (PPSV)
- Pneumococcal conjugate vaccines (PCV)

• Meningococcal

- A, C, Y and 135 (Mecevax ACWY)
- A, CX, Y, and 135 DT conjugate (Meningococcal A and C).

Antigens of different pathogens

- DTwP (triple antigen, triplevac, comvac 3)
- DTaP (Boosterix, Adacel)
- DTwP + Hib - Quadrivalent (easy 4, triple antigen + HibPro, Quadrovax, Shan 4, TetractHib)
- DTwP + Hep B (Qvac, Comvac 4-hep B, Tripvac hep B, Tritanrix ep B, Shantetra)
- DTaP + Hib (Infanrix + Hiberix, Tripacel + ActHib)
- DTwP + Hep B + Hib - Pentavalent Pentavac, Easy 5, Shan 5 Covac 5)
- DTaP + Hib + IPV (Pentaxim)
- Hep B + Hep A (Twinrix)

Combination vaccines not yet licensed in India**• DTwP + IPV**

This combination vaccine is in use since 1990 in countries where polio stands eradicated and inactivated (killed) polio vaccine is being employed. In India, we are still predominantly using OPV.

- DTwP + IPV + Hib
- DTaP + IPV
- DTaP + Hep B
- DTaP + IPV + Hep B
- DTaP + Hib + Hep B
- DTaP + IPV + Hep B + Hib

• Varicella + MMR

- Hep A + Typhoid
- Hep B + Hib MMRV

Abbreviations: Hep B, hepatitis B; Hep A, hepatitis A; Hib, hemophilus influenza type b; OPV, oral vaccine; IPV, inactivated polio vaccine; MMR, measles mumps and rubella; DTwP, diphtheria tetanus (whooping cough) and pertussis; DTaP, diphtheria tetanus (acellular) pertussis.

Multiple Choice Questions

1. An otherwise healthy infant develops axillary lymphadenitis without suppuration following BCG vaccine. What shall be your approach?
 - A. INH
 - B. Surgical excision
 - C. Antimicrobial therapy
 - D. Wait and watch
2. Spot the vaccine that may cause pseudotumor cerebri:
 - A. IPV
 - B. DTP
 - C. PCV
 - D. MMR
3. Rotavirus vaccine should never be given after the age of:
 - A. 20 weeks
 - B. 24 weeks
 - C. 32 weeks
 - D. 36 weeks
4. Spot the wrong observation regarding adverse events following immunization:
 - A. Very infrequently, DTP may cause hypotonia-hyporeflexia in children
 - B. Occasionally IPV may cause polio-like illness
 - C. Vitamin A overdose may cause pseudotumor cerebri
 - D. Measle-like illness some days after the measles vaccine
5. Pick up the incorrect entry:
 - A. Three vital elements in successful cold chain are: cold chain equipment, transportation, and motivated and trained manpower for maintaining the link
 - B. Diluent should be kept in the lowermost compartment of the refrigerator
 - C. Hib, pneumococcal, Vi typhoid and meningococcal vaccines are conjugated vaccines
 - D. MMR was introduced in India's national schedule in 2012

Answers

1. D 2. B 3. C 4. B 5. D

Clinical Problem-solving

Review 1

A baby born preterm (at 34 weeks) to a primigravida, needs resuscitation. After 4 days of birth, his problem of hypoglycemia and hypothermia stands resolved and he is feeding well on mother's breast. His birthweight is 1.6 kg.

1. What should be your recommendation for BCG vaccine?
2. How about OPV?
3. Will the same recommendation do in case of hepatitis B vaccine?

Review 2

A toddler has had all IAP-recommended vaccines, except conjugated typhoid vaccine which was supposed to be given at 9–12 months age. Now aged 18 months, he received MMR, DTP, varicella, PCV, Hib and IPV during the past 3 months.

1. What should be done for conjugated typhoid vaccine that was missed?
2. What about its booster?
3. What is the alternative advice if conjugated vaccine is not available?

Answers

Review 1

1. BCG should be given to this preterm baby as usual.
2. OPV should also be given to this preterm baby as usual.
3. Since the baby's weight is less than 2 kg, it is advisable to withhold the hepatitis B vaccine for the time being in view of the suboptimal immunogenicity. This should be given when the baby is one month old. Alternatively, it may be given at the time of discharge provided that baby weight gain is good.

Review 2

1. Since the toddler is still <2 years of age, he cannot be given V1-polysaccharide vaccine. He should, therefore, be offered the conjugate vaccine (Typbar-TCV) for early protection.
2. Booster of Typbar-TCV is required to be given at 2 years of age.
3. Alternatively, let the child cross age of 2 years when the polysaccharide vaccine can be given. This vaccine needs to be repeated every 3 years for sustained protection.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS/INTERNET

1. Gupte N, Gupte S. Adverse events following immunization: Issues and concerns. *Recent Advances in Pediatrics (Special Vol. 27: Infectious Diseases-II)*. New Delhi: Jaypee In press.
2. Vashishtha VM, Kumar P. 50 years of immunization in India: Progress and future. *Indian Pediatr* 2013;50:111–118.

BOOKS/MONOGRAPHS

1. Government of India. *National Vaccine Policy*. New Delhi: Ministry of Health and Family Welfare 2013. Available at: [http://mohfw.nic.in/WriteReadData/1892s/108481197NATIONAL % VACCINE % POLICY % 20 BOOK. pdf](http://mohfw.nic.in/WriteReadData/1892s/108481197NATIONAL%20VACCINE%20POLICY%20BOOK.pdf). Accessed on: 15 May 2015.
2. Indian Academy of Pediatrics Advisory Committee on Vaccines and Immunization Practices (ACVIP). *IAP Guidebook on Immunization 2013–14*. Gwalior: IAP National Publication House 2014.
3. Vashishtha VM, Kalra, A, Thacker N. *FAQs on Vaccines and Immunization Practices* New Delhi: Jaypee 2011.

INTRODUCTION

Adequate nutrition is of paramount importance during childhood, especially in the first three years of life, when growth is most rapid and the child is, by and large, totally dependent on his caretaker(s), usually the parents. Since an important factor responsible for adequate growth is balanced nutrition, erroneous nutrition leads to poor weight gain, undernutrition and inadequate growth. Naturally, a basic knowledge of nutritional requirements at various ages as also sources of vitamins and other micronutrients and minerals is mandatory.

CERTAIN DEFINITIONS

The term, **energy requirement**, denotes the amount of dietary energy required to balance energy expended and deposited in new tissues (growth). Table 11.1 gives the break-up of energy expenditure.

In order to meet the growth needs in first three years and during adolescence, a higher energy dense diet (less complex carbohydrates and larger quantity of fat) is needed. Seven principle classes of nutrients are—carbohydrates, fats, proteins, fiber, mineral, vitamins and water. Leaving aside fiber, the remaining six are the chief constituents of food. These six factors form the human body in the following way:

- **Water:** 63%
- **Proteins:** 17%
- **Fats:** 12%
- **Carbohydrates:** 1%
- **Vitamins and minerals:** 7%.

The term, **macronutrients**, refers to carbohydrates, fats and proteins—the building blocks of the body that are needed in large amounts (g).

The term, **micronutrients**, denotes vitamins and minerals that are needed in only very small amounts (µg, mg). Their role in enhancing immunity and in various metabolic pathways as cofactors is indispensable.

The term, **recommended dietary allowance**, refers to recommended daily levels of nutrients estimated to be

Table 11.1: Break-up of energy expenditure

Growth	12%
Physical activity	25%
Basal metabolism	50%
Fecal loss	8%

Table 11.2: Daily requirement for water

Age range	Water requirement (mL/kg)
First 3 days	80–100
3–10 days	125–150
15 days–3 months	140–160
3–12 months	150
1–3 years	125
4–6 years	100
7–9 years	75
10–12 years (and thereafter)	50

sufficiently high to meet the physiologic needs of nearly all healthy individuals in a particular age and gender group. Alternative terms used include **daily requirement**, **safe intake of nutrients** and **recommended daily amounts of nutrients**.

WATER

It is second only to oxygen as a must for survival. Compared to adults, infants require much larger amount of water per unit of body weight. Its requirements at different ages are given in Table 11.2.

CARBOHYDRATES (ENERGY)

Carbohydrates, the major source of energy (4 kcal/g), add up to the bulk (55–60%), taste and texture of the diet. Two types are known:

1. **Simple:** Monosaccharide, disaccharides, e.g. glucose, fructose (sucrose in sugar, lactose in milk), fruits, vegetables.
2. **Complex:** Oligosaccharides, polysaccharides, e.g. starch, pulses, millets, roots.

With the exception of fiber, all carbohydrates are converted to glucose which is either employed as a fuel by the brain and muscles or stored in liver and muscles as glycogen. Carbohydrates consumed in excess are converted to fat.

Glucose from starch and sugar in diet constitute the main source of energy. The cells use glucose as a fuel. The liver and muscles convert it to glycogen. Excess carbohydrates are converted to fat.

Calorie or energy requirement varies from age to age as is shown in Tables 11.3 and 11.4. On an average, 50% of calories should come from carbohydrates, 35% from fats and 15% from protein.

Table 11.3: Daily calorie requirement of infants

Age range (months)	Requirement (cal/kg)
0–3 months	120
3–6 months	115
6–9 months	110
9–12 months	105

Table 11.4: Daily requirement for calories

Age range (years)	Requirement (Kcal/kg)
Under 1 (average)	110
1–3	100
4–6	90
7–9	80
10–12	70
13–15	60
16–19	50
Adult	40

Table 11.5: Absolute daily requirement for calories during first year

Age (months)	Calorie requirement
1	500
2	600
4	700
5	800
9	900
10	1,000

Table 11.6: Holliday and Seger formula for daily calorie and fluid calculations

Weight range	Calories	Fluids
3–10 kg	100 kcal/kg/day	100 ml/kg/day
10–20 kg	1000 + 50 kcal/kg/day for each kg >10 kg	1000 + 50 ml/kg/day for each kg >10 kg
20 kg	1500 + 20 kcal/kg/day for each kg >20 kg	1500 ml/kg/day for each kg >20 kg

It is worth remembering that daily requirement is 100–120 kcal/kg for the first year of life. During the subsequent period, it decreases by around 10 kcal/kg for each succeeding three year duration.

Table 11.5 presents the total daily calorie requirement during the first year of life. An infant of one year of age needs about 1,000 kcal. A rough rule is to add 100 calories per each year of age upto a maximum of 1,500 kcal. About adolescence; when the growth spurt occurs, calorie needs are much higher. According to this rule a child of five years of age needs 1,000 + 400 = 1,400 kcal. Calculations according to another widely-employed formula (Holliday and Seger formula) are given in Table 11.6. Box 11.1 gives the break-up of energy requirement.

Box 11.1 Break-up of energy requirement

- Maintenance of basal metabolism: 50%
- Specific dynamic action: 5%
- Growth: 12%
- Physical activity: 25%
- Losses in stools, etc.: 8%

PROTEINS

Proteins of animal origin are termed **biologically complete proteins** since these provide a good deal of essential amino acids, namely—lysine, leucine, isoleucine, tryptophan, valine, methionine, phenylalanine, threonine and histidine. On the contrary, proteins of vegetable origin are usually **biologically incomplete** since they lack one or more of the essential amino acids. However, when different vegetable sources of protein are combined, result is a product that is likely to provide all the essential amino acids. Higher amounts of vegetable proteins are needed to make allowance for low biological value (Table 11.7).

Biologic value (BV) is defined as the fraction of absorbed nitrogen retained in the body for growth or maintenance. It is 100 for egg protein which is regarded as the **reference protein**, 75 for milk and fish and 67 for rice. Energy value of protein is four kcal/g. Protein quality is judged by biologic value, true digestibility and net protein utilization (NPU) (Box 11.2).

Egg protein is considered a **reference protein** on account of its highest BV and NPU (Box 11.3, Fig. 11.1). Since egg protein BV is taken as 100%, other foods are expressed in relation to this value. As a rough rule, animal proteins possess higher BV than plant protein.

Table 11.7: Daily requirement for proteins

Age range (years)	Protein requirement (g/kg)
Under 1	2.6–3.5
1–3	2.0–2.5
4–6	3.0
7–9	2.8
10–12	2.0
13–15	1.7
16–19	1.5
Adult	1.0

Box 11.2 Protein quality indices

$$\text{Biologic value (BV)} = \frac{\text{Nitrogen retained}}{\text{Nitrogen absorbed}} \times 100$$

$$\text{True digestibility (TD)} = \frac{\text{Nitrogen absorbed}}{\text{Nitrogen intake}} \times 100$$

$$\text{Net protein utilization (NPU)} = \frac{\text{True digestibility}}{100} \times \text{Biologic value}$$

Box 11.3 Nutritive value of an average-size hen's egg

- | | |
|------------------|------------|
| • Fat (6g) | 24 kcal |
| • Proteins (6g) | 58 kcal |
| • Carbohydrates | Negligible |
| • Total calories | 78 kcal |
| • Cholesterol | 200 mg |
| • Sodium | 65 mg |

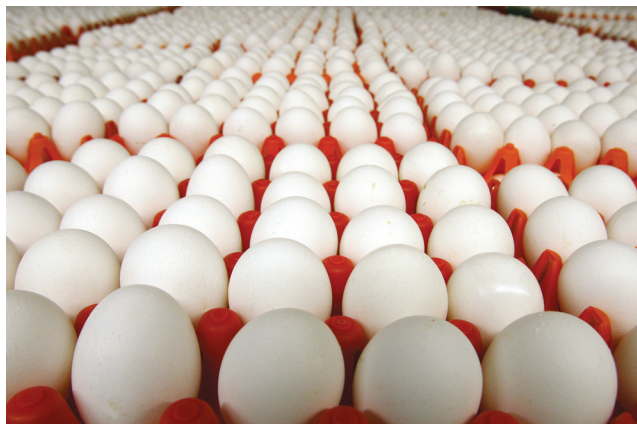


Fig. 11.1: Egg protein has highest biological value and hence considered a standard reference protein. On an average, one hen's egg provides 6 g protein (24 kcal), 6 g fat (54 kcal) and a total energy of 78 kcal. Egg yolk is full of fat with a cholesterol content of 200 mg.

FIBER

DEFINITION

Fiber is a non-starch polysaccharide that is non-digestible, but that helps in digestion of food stuffs. It is a constituent of plant cell and forms bulk of diet. Its food value is negligible.

FIBER-CONTAINING FOODS

Important fiber-containing foods include:

- Cereals—whole wheat in particular
- Pulses and legumes
- Sprouted seeds
- Nuts—groundnut, walnut, almonds
- Fruits—whole fruits in particular
- Vegetables, including dried beans, green-leafy vegetables (GLV) in particular.

TYPES

Two types are:

1. **Fibrous:** Cellulose, hemicellulose, lignin
2. **Viscous:** Pectins, gums, mucilages.

ADVANTAGES

- It forms the stool bulk which is important for normal functioning of the gut, including proper movements.
- It is important for preventing and even curing chronic constipation.
- It promotes satiety (stomach contentment).
- It prevents hypercholesterolemia.
- It slows down gastric emptying.
- It flattens glucose tolerance curve.
- It decreases blood glucose level in diabetics.
- It enhances water-holding capacity of gut.
- It safeguards against colonic cancer and diverticulitis.

DISADVANTAGE

Very high fiber intake may interfere with bioavailability of minerals (e.g. calcium-deficiency rickets).

DAILY REQUIREMENT

- **Infants and children:** 300–400 mg/kg/day
- **Adolescents:** Around 30–40 g/day.

FATS

- Whereas carbohydrates are readily available source of energy, fats constitute concentrated energy-giving element, thereby enhancing the calories without much increase in bulk. The minimal requirement is not accurately defined.
- Over and above being major source of energy, fats carry fat-soluble vitamins A, D, E and K and are precursors of hormones and prostaglandins.
- Usually upto 30% of total energy should be from fats (3.5% of calories should be supplied by linoleic acid and 0.3% from linolenic acid). Since human body is incapable of synthesizing this acid, it has got to be supplied in diet. Its deficiency in infants causes dryness and thickening of the skin with desquamation and intertrigo.
- Important lipids are:
 - Triglycerides (fats and oils)
 - Phospholipids (lecithin) and
 - Sterols (cholesterol).
- Depending on the length of the carbon, triglycerides may be:
 - Short-chained
 - Medium-chained triglycerides (MCT)
 - Long-chained triglycerides (LCT)
- Depending on the saturation, triglycerides may be:
 - **Saturated:** Obtained from meat and coconut oil. Human body can also produce them from carbohydrates and proteins.
 - **Unsaturated:** Monounsaturated and polyunsaturated, obtained from vegetables, nuts and seeds.
- Whereas monounsaturated fatty acids (MUFA) such as oleic acid may also be produced by the body, polyunsaturated fatty acids (PUFA), also called **essential fatty acids** (EFA), must be provided by the dietary sources. PUFA consists of omega-6 fatty acids (linoleic acid, arachidonic acid) present in normal balanced diet and omega-3 fatty acids e.g. linolenic acid, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which are present in fish and seafood.
- EFAs deficiency manifests as growth failure, alopecia, diarrhea, and fragile bone from decreased calcium absorption and deposit in bones.
- Lecithin is a major component of cell membrane. It is synthesized by the liver.
- Cholesterol, an important component of cell membrane, may be produced by the human liver. Additionally, its dietary sources include animal fats (egg, meat especially kidney and liver, cheese, desi ghee). It may be transformed to hormones, vitamin D and bile. The daily intake of cholesterol should not exceed 250–300 mg. Just one egg provides near 200–250 mg of cholesterol. Hence consumption of more than one full egg/day is not rationally good.
- Energy value of fats is 9 kcal/g. No more than 7% total fats in diet should be saturated.

DEFINITION

Glycemic index (GI) is defined as the extent of ability of a carbohydrate item to raise blood glucose level. Hence, higher the glycemic index of a carbohydrate foodstuff, more is the chance of its making a rapid rise in blood glucose level. Likewise, lower the GI of a carbohydrate foodstuff less is the chance of its making a rapid rise in blood glucose level.

High GI foodstuffs include glucose and rice. The low GI foodstuff includes wheat, maize and pulses. These food items are preferred for diabetic patients.

ADVANTAGES OF LOW GLYCEMIC INDEX FOOD ITEMS

- Supply and maintenance of blood glucose level for longer time, resulting in prolonged physical endurance.
- Reduction in hunger.
- Facilitation of reduction in weight.
- Reduction in blood glucose level.
- Increased sensitivity to insulin.
- Reduced risk of cardiovascular disease.

VITAMINS

Table 11.8 summarizes the requirements of vitamins which are essential for maintenance of good health.

MINERALS AND MICRONUTRIENTS/
TRACE ELEMENTS

Cations like calcium, magnesium, sodium, potassium and anions like phosphorus, sulfur and chloride which are needed in amounts exceeding 100 mg/day are called **macrominerals**.

Elements like iron, zinc, copper, cobalt, iodine, selenium, molybdenum and chromium which are needed in very small amounts (upto 100–200 µg/g matrix) are called **microminerals**, **micronutrients** or **trace elements**.

Table 11.8: Daily requirement for vitamins

Vitamins	Requirement
A	1,500–5,000 IU
B, (thiamine)	0.5–1.5 mg
B ₂ (riboflavin)	0.5–2.5 mg
Niacin (ninacinamide, nicotinamide, nicotinic acid)	0–2 mg
B ₆ (pyridoxine)	0.4–1.4 mg
B ₁₂ (cyanocobalamin)	1–1.5 µg
Folic acid	25–1000 µg
C	30–50 mg
D	400 IU
E	4–5 IU

Abbreviation: IU, international unit.

Table 11.9: Daily requirement for minerals

Mineral	Requirement
Iron	<ul style="list-style-type: none"> • Infants: 1mg/kg (6–10 mg) • 1–years: 15 mg • 3–12 years: 10 mg • 12–18 years: 18 mg
Calcium	<ul style="list-style-type: none"> • Infants: 400–600 mg • 1–10 years: 0.7–1.0 g • Over 10 years: 1.2–1.5 g
Magnesium	<ul style="list-style-type: none"> • Infants: 40–70 mg • 1–3 years: 100–150 mg • 3–12 years: 200–300 mg • 12–18 years: 300–350 mg
Potassium	1.5 mEq/kg (1–2 g)
Sodium	2.0 mEq/kg
Zinc	0.3 or more mg/kg
Iodine	0.2 mg
Copper	0.05–0.1 mg/kg
Fluorine	0.5–1 mg

The recommended intake of important minerals is given in Table 11.9. Table 11.10 lists salient features of important minerals.

IRON

Iron, available from food, is of two types, namely—**heme** and **nonheme**. Heme iron is found in nonvegetarian foods, say meat, liver, chicken and fish. Around 15–35% heme iron gets absorbed from the gut. Nonheme iron is present in plants, legumes, eggs, milk and cereals. Its absorption is much less, i.e. hardly 1%. Several factors influence its absorption (Table 11.11). During adolescence, iron needs enhance. This is especially true in case of menstruating teenagers.

ZINC

Zinc is normally present in our body in sufficient amount. No supplementation is, therefore, required by healthy individuals. In certain situations, say diarrhea (especially persistent diarrhea), malnutrition, infantile tremor syndrome (ITS), and acrodermatitis enteropathica, zinc deficiency coexists. Therefore, zinc supplementation is strongly recommended to hasten recovery in these conditions. Normal daily requirement of zinc is 4–6 mg/day. Excess of zinc intake may be complicated by copper deficiency.

FREE RADICALS AND ANTIOXIDANTS

FREE RADICALS CAUSING TISSUE DAMAGE

The term, **free radicals** refers to atoms or molecules that contain one or more unpaired electrons that are capable of altering (usually enhancing) their chemical reactivity and cause tissue damage. These are produced in large amounts during all tissue activities (infection, phagocytosis, tissue injury, and ischemia-perfusion). Examples of free radicals are superoxide anions, singlet oxygen, peroxide anion, hydroxyl

Table 11.10: Salient features of important minerals/trace elements/micronutrients

Mineral/trace element	Source	Deficiency	Excess
Iron	Green vegetables, meat, yolk, whole grains, nuts, legumes, milk, especially, breastmilk, is a poor source.	Microcytic-hypochromic anemia	Hemosiderosis, poisoning
Zinc	Cheese, nut, grains, meat, fish	Dwarfism with iron-deficiency anemia, hyperpigmentation, hepatosplenomegaly, hypogonadism, acrodermatitis enteropathica: poor wound healing, depressed immunocompetence, ITS, LBW	Gastrointestinal upset, copper deficiency, reduced high density lipoprotein
Copper	Legumes, nuts, whole grains, meat, live, oyster (shell-fish)	Refractory anemia, osteoporosis, neutropenia, depigmentation, ataxia, raised serum cholesterol	ICC
Magnesium	Cereals, legumes, nuts, meat, milk	Tetany	None
Calcium	Milk and its products, fish, green leafy vegetables	Tetany, rickets	Renal stones, heart block
Phosphorus	Milk and its products, fish, green leafy vegetables	Rickets	Tetany
Iodine	Seafood, vegetables from iodine-rich soil, iodized salt	Goiter, cretinism	Goiter
Fluoride	Seafood, tea	Dental caries	Fluorosis
Chromium	Drinking water, animal foods, yeast	Impaired glucose tolerance, diabetes mellitus in animals	None

Abbreviations: ITS, infantile tremor syndrome; LBW, low birth weight; ICC, Indian childhood cirrhosis.

Table 11.11: Foods affecting absorption of iron from the gut

Absorption enhanced	Absorption reduced
Vitamin C-rich foods <ul style="list-style-type: none"> Guava Lemon Orange Indian gooseberry 	<ul style="list-style-type: none"> Tea Coffee Maize Phytates (whole meal bread)
Foods containing heme iron <ul style="list-style-type: none"> Liver Meat Chicken Fish 	
Fermented/germinated foods	

radical and hydrogen peroxide. Excess of free radicals results either from their higher production or from inadequate antioxidant defense. Disorders in which free radicals appear to play a significant role are listed in Box 11.4.

ANTIOXIDANTS

To counter the free radicals, defenses are provided in the form of antioxidants which are defined as substances in food that significantly decrease the adverse effects of free radicals. Examples of antioxidants are superoxide dismutase, transferrin, glutathione peroxidase, vitamin C (ascorbic acid), vitamin E (tocopherol), β -carotene, selenium, zinc, iron, manganese, nicotinamide, riboflavin and lycopene.

Box 11.4

Free radicals in the pathogenesis of various disorders

- Retinopathy of prematurity
- Rh hemolytic disease
- Hemolytic anemia of the newborn
- HIE
- IVH
- BPD
- ARDS
- Cystic fibrosis
- NEC
- IBD
- Rheumatoid arthritis
- Severe edematous PEM (kwashiorkor)
- Cholestatic liver disease
- Pancreatitis
- Iron-overload (hemochromatosis)
- Copper-overload (Wilson disease, ICC)
- Storage disorders
- Malignancies.

Abbreviations: HIE, hypoxic-ischemic encephalopathy; IVH, intraventricular hemorrhage; BPD, bronchopulmonary dysplasia; ARDS, acute respiratory distress syndrome; NEC, necrotizing enterocolitis; IBD, inflammatory bowel disease; PEM, protein energy malnutrition; ICC, Indian childhood cirrhosis; Rh, rhesus disease.

Recently, a number of synthetic antioxidants N-acetyl cysteine (NAC), glutathione, glutathione peroxidase analogue (ebselen), coenzyme Q derivatives and superoxide dismutase are available. These are yet to be successfully tried in humans.

178 Types of antioxidants are:

- **Intracellular antioxidant:** Superoxide dismutase and glutathione peroxidase.
- **Extracellular antioxidant:** Transferrin, haptoglobin, albumin, extracellular superoxide dismutase and catalase, bilirubin, mucus, glucose, vitamin C, urate.
- **Lipoprotein antioxidant:** Vitamin E, beta-carotene, retinyl stearate and lycopene.
- **Membrane antioxidant:** Vitamin E, beta-carotene and coenzyme O.
- **Nutritional antioxidants:** Vitamin E (tocopherols and tocotrienols), beta-carotene, vitamin C, phytochemicals like flavonoids, flavones, flavanols, cinnamic acid, coumarin derivatives, phytoalexin derivatives and selenium as a cofactor for glutathione peroxidase, cysteine, taurine.
- Selenium compounds like glutathione peroxidase, food additives like propyl gallate, butylated hydroxyanisole, antioxidant drugs like allopurinol, desferrioxamine and NAC.

Experience has shown that several exogenous substances such as natural dietary components (β -carotenoids, vitamin E, vitamin C, selenium) and pharmaceutical agents (desferrioxamine, allopurinol) can function as antioxidants. However, so far exogenous supplementation of antioxidants is yet to establish its clear-cut role in prevention of disease. Nutritionists, therefore are of the opinion that a mixed well-balanced diet, vegetables, fruits that supply vitamins and other micronutrients is the most feasible and the best way to ensure a sufficient supply of antioxidants.

IMMUNONUTRITION

(Nutrition Pharmacology, Nutrition Pharmacotherapy)

DEFINITION

Over the years, the concept of employing nutrients for improving the immune function of the body has come of age. Immunonutrition (IMN), a relatively new concept, is defined as enteral feeding formulas supplemented with immunonutrients comprising of amino acids, antioxidants, micronutrients and probiotics, etc. aimed at providing beneficial effects of enhanced immune function and, thereby cutting down risk of infectious complications.

COMMONLY-EMPLOYED IMMUNONUTRIENTS

The most commonly employed and researched immunonutrients are:

- Amino acids—arginine (a nonessential amino acid), glutamine (precursor for nucleotide),
- Nucleotides,
- Fatty acids—omega-3 polyunsaturated fatty acids,
- Taurine,
- Vitamins—A, C and E,

- Micronutrients—iron, zinc, selenium,
- Prebiotics and probiotics.

Till date, most experience revolves around **glutamine supplementation**. Glutamine is a precursor for nucleotide synthesis, a substrate for liver gluconeogenesis and an important fuel source for cell with rapid turnover, say gastrointestinal epithelium, lymphocytes, fibroblasts, reticulocytes, etc.

Arginine, a nonessential amino acid, is a conditionally essential amino acid during catabolic states such as sepsis and trauma (just like glutamine). It has a wide range of biological actions that are beneficial to the body.

ROLE

- **Nucleotides** play a key role in T-cell function and cell-mediated immunity.
- **Omega-3 fatty acids** (linolenic acid), found in fatty fish oil, has considerable effect on the immune system in the form of immunologic benefit and anti-inflammatory effect.
- **Taurine** is a conditionally semi-essential amino acid in neonates, especially preterms. Currently, it is employed in most infant formulas.
- **Vitamins** A, C, E and micronutrients, iron, zinc, selenium are well known for their immunologic role.
- **Prebiotics and probiotics** exert their beneficial immunologic effect by varied mechanisms, including enhancement of the mucosal immune defense.

ADMINISTRATION

Immunonutrients having favorable effect on the immune system are added to standard nutritional support solutions for deriving immunological benefits. They are usually administered in supranormal doses enterally. At times, they may be added parenterally for modulating response to surgery, trauma or sepsis.

INDICATIONS

Undoubtedly, immunonutrition has the potential to cut down morbidity and mortality in critically ill children with

- Gastrointestinal diseases—inflammatory bowel disease (IBD),
- Immune deficiency disorders,
- Polytrauma, and
- Sepsis.

There is an evidence that immunonutrition may have a promising role in cancer prevention.

FUTURE PROSPECTS

Immunonutrition has bright prospects and potentials for cutting down morbidity and mortality in critically ill children with the above indications. Nevertheless, more work is warranted to establish their efficacy and safety in children.

DIETARY INTAKE BY CHILDREN: INDIAN SCENARIO

Survey conducted by the National Nutrition Monitoring Bureau (NNMB) indicates that diet of the Indian preschoolers is grossly deficient in each and every category of food (Table 11.12).

Overall, it is the deficiency of calories (energy), whereas protein intake is, by and large, satisfactory. A noteworthy observation is that diet of children belonging to the higher strata of society show intake of protein that is in excess. It is, therefore, important to lay stress on total intake of food rather than just protein as is often done in practice.

Table 11.13 presents the recommended balanced diets for children. Table 11.14 gives the nutritive value of some commonly used foods in India as per the ICMR with minor modifications. Fruits, vegetables and nuts and seeds are rich in vitamins, micronutrients, minerals, antioxidants and fiber (Figs 11.2 to 11.6).

Table 11.12: National Nutrition Monitoring Bureau (NNMB) survey data on actual *vis-a-vis* recommended dietary consumption by Indian preschoolers as per Indian council of Medical Research (ICMR) document

Dietary item	Actual intake	Recommended intake
Cereals (g)	147	150–200
Pulses (g)	16	40–50
Leafy vegetables (g)	4	50–75
Other vegetables (g)	14	30–50
Fruits (g)	7	40–50
Milk and milk products (g)	80	200
Fats and oils (g)	4	20–25
Flesh foods (g)	4	30
Sugar and jaggery (g)	5	30–40
Calories (kcal)	758	1200–1700
Protein (g)	22–30	22–30
Iron (mg)	6.9	11.5–18.4
Calcium (mg)	193	400
Vitamin A (mg)	220	400
Riboflavin (mg)	–	0.7–1.0

Table 11.13: Balanced diets for children

	Preschool children				School children			
	1–3 years		4–6 years		7–9 years		10–12 years	
	Veg. (g)	Nonveg. (g)	Veg. (g)	Nonveg. (g)	Veg. (g)	Nonveg. (g)	Veg. (g)	Nonveg. (g)
Cereals	150	150	200	200	250	250	320	320
Pulses	50	40	60	50	70	60	70	60
Green leafy vegetables	50	50	75	75	75	75	100	100
Other vegetables/roots and tubers	30	30	50	50	50	50	75	75
Fruits	50	50	50	50	50	50	50	50
Milk	300	200	250	200	250	200	250	200
Fats and oils	20	20	25	25	30	30	35	35
Meat fish and eggs	–	30	–	30	–	30	–	30
Sugar and jaggery	30	30	40	40	50	50	50	50

Table 11.14: Nutritive value of commonly used food (per 100 g)

Foodstuffs	Calories	Proteins	Foodstuffs	Calories	Proteins
Cereals			Nuts		
• Wheat	346	11.8	• Coconuts (dry)	662	6.8
• Rice	346	6.5	• Cashew nut	596	21.2
• Maize	325	4.7	• Groundnut	549	26.7
• Wheat-flour	348	11.0	• Apple	55	0.3
• Soyabean	432	43.2	• Pineapple	46	0.4
• Green gram	348	24.5	• Orange	53	0.3
• Black gram (dal)	347	24.0			
Pulses			Fruits		
• Bengal gram (whole)	360	17.1	• Guava	51	0.9
• Bengal gram (dal)	372	20.8	• Tomato (ripe)	20	0.9
• Peas (dry)	315	19.7	• Pomegranate	65	1.6
			• Apricot	51	0.6
			• Mango (ripe)	53	1.0
			• Lemon	57	1.0
			• Litchi	61	1.1

contd...

Foodstuffs	Calories	Proteins	Foodstuffs	Calories	Proteins
Leafy vegetables			Flesh foods		
• Onion tops	61	4.7	• Egg	173	13.5
• Spinach	26	2.0	• Goat meat	118	21.4
• Mustard leaves	34	4.0	• Mutton	194	18.5
• Cabbage	27	1.8	• Chicken	300	25
• Cauliflower leaves	67	5.9	• Fish	80–100	18–20
Roots and Tubers			Milk products		
• Onion	49	1.4	• Cow's milk	66	3.2
• Carrot	48	0.9	• Buffalo's milk	110	4.3
• Potato	97	1.6	• Human milk	66	1.1
• Turnip	29	0.5			
Other vegetables			Miscellaneous		
• Amla (Indian gooseberry)	58	0.5	• Bread	245	7.8
• Cauliflower	30	2.6	• Sago	351	0.2
• Pumpkin	25	1.4	• Sugar	398	0.1
• French beans	48	3.8	• Jaggery	383	0.4
			• Oil or ghee	900	Nil



Figs 11.2A and B: Fruits are a rich source of vitamins, minerals and antioxidants.



Fig. 11.3: Bananas are a rich source of carbohydrates (energy); orange and other citrus fruits provide plenty of vitamins C.



Fig. 11.4: Vegetables—a rich source of vitamins and minerals.



Fig. 11.5: Dark green leafy vegetables (amaranthal, spinach {palak}) are a rich source of minerals (iron, zinc, calcium, phosphorous, potassium), vitamins (A, K, B-complex, C, E, folate), fiber and antioxidants. Spinach has been designated as the world's healthiest vegetable.



Fig. 11.6: Mixed nuts and seeds are rich in unsaturated fat and vitamin E.

Multiple Choice Questions

- Spot the wrong entry:
 - Energy requirement for maintenance of basal metabolism is 50%
 - Energy requirement for a healthy 1-month-old infant is 500 kcal
 - On an average, a 1-year-old child needs 1000 kcal/daily
 - Of the 6 factors, carbohydrates form 7% of human body
- All of the following observations about protein are correct, except:
 - Proteins of vegetable origin are usually biologically incomplete
 - Egg protein is considered a reference protein
 - Biological value for milk is 90 and for fish 67
 - Protein requirement <1 year is 2.6–3.5 g/kg/day
- All of the following observations about fats are correct, except:
 - Fats carry fat-soluble vitamins (A, D, E and K) are precursors of hormones and prostaglandins
 - Usually upto 25% of energy should come from fats
 - Polyunsaturated fatty acids (PUFA) must be provided by the dietary sources
 - One egg provides near 200–250 mg of cholesterol
- Which of the following statements is incorrect:
 - The low glycemic index foodstuff (wheat, maize and pulses) are recommended for diabetic patients
 - Vitamin C-rich foods include guava, lemon, orange, and Indian goose berry
 - Heme iron is found in nonvegetarian foods, say meat, liver, chicken and fish
 - Around 75% heme iron gets absorbed from the gut
- Spot the correct statement:
 - Antioxidants are substances in food that significantly decrease the adverse effects of free radicals
 - Rice is known for its highest glycemic index
 - Fruits are not a good source of vitamins, minerals and antioxidants
 - Mixed nuts and seeds are rich in saturated fats

Answers

1. D 2. C 3. B 4. D 5. A

Clinical Problem-solving

Review 1

A 7-year-old child presents with poor appetite and generalized weakness. His weight is 18 kg and height 113 cm. By recall method, he is consuming 1400 kcal and 50 g protein daily on an average.

- Is this intake of energy and protein sufficient for his age? If no, how much should it be?
- How have you reached the figures of 1800 kcal and 62 g protein?
- Would not it be all right to schedule this child's recommended intake chart according to his actual weight?

contd...

Review 2

A teenager athlete is upset that on account of his being a vegetarian, he was on a biologically incomplete protein diet. Since he was unlikely to get converted to a nonvegetarian, his concern appeared to be well-founded.

1. What is way out for this young boy?
2. What indeed is meant by biological value?
3. How is biological value judged?
4. Which foodstuff has the highest biological value?

Answers**Review 1**

1. No. Recommended dietary intake at this age is around 1600 kcal and 62 g protein. Thus, the child is falling short of 200 kcal and 13 g protein in his daily dietary consumption.
2. Basic calorie requirement for a child of 1 year is 1000 kcal. For every subsequent year he needs additional 100 kcal until adolescent spurt. Thus requirement at 2 year-1100 kcal, 3 years-1200 kcal, 4 years-1300 kcal, 5 years-1400 kcal, 6 years-1500 and 7 years-1600 kcal.
As regards protein, requirement at 7 years is around 2.8 g/kg/day. Since standard weight at 7 years is 22 kg, his total requirement of protein comes to nearly 62 g.
3. No. His recommended intake should target his standard (expected) weight for age. Only then he will be able to catch up. Else, state of undernutrition shall continue.

Review 2

1. True, proteins of animal origin are termed biologically complete proteins. Reason? They provide a good deal of essential amino acids, namely—lysine, leucine, isoleucine, tryptophan, valine, methionine, phenylalanine, threonine and histidine. Proteins of vegetable origin are usually biologically incomplete since they lack one or more of the essential amino acids. Yet, there is a way out for this boy. When different vegetable sources of protein are combined, result is a product that is likely to provide all the essential amino acids. Higher amounts of vegetable proteins are needed to make allowance for low biological value.
So, this boy get make up his deficiency but consuming higher amounts of varying vegetable sources of proteins in combination.
2. Biologic value is the fraction of absorbed nitrogen retained in the body for growth or maintenance. It is 100 for egg protein which is regarded as the reference protein, 75 for milk and fish and 67 for rice. Energy value of protein is 4 kcal/g.
3. Protein quality is judged by biologic value, true digestibility and net protein utilization (NPU) (Box 11.2).
4. Egg protein is considered a reference protein on account of its highest BV and NPU. Since egg protein BV is taken as 100%, other foods are expressed in relation to this value. As a rough rule, animal proteins possess higher BV than plant protein.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

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OVERVIEW

Infant and young child feeding is of great importance. It is a must to meet nutritional as well as emotional and psychological needs of the infant. The basic food for infant feeding is human milk. Breastfeeding is the most natural method and, in fact, the supreme gift. Most appropriate feeding strategy for infants and young children is:

- Early initiation of breastfeeding.
- Exclusive breastfeeding for first six months.
- Continuation of breastfeeding for upto two years and, if workable, even beyond.
- Addition of adequate complementary foods after completion of 6 months.

Following these recommendations in letter and spirit is crucial for the proper growth and development of infants and children and for reducing the prevalence of malnutrition which directly or indirectly leads to high morbidity and mortality.

IMPORTANT DEFINITIONS

- **Exclusive breastfeeding:** Infant receiving only breast milk from his or her mother or wet nurse or expressed breast milk and no other liquids or solids; not even water with exception of oral rehydration solution (ORS), multivitamins or mineral supplements and medicines prescribed by the doctor.
- **Predominant breastfeeding:** Infant's predominant source of nourishment has been breast milk (including milk expressed or from a wet nurse as the predominant source of nourishment). However, the infant may also have received liquids (water and water-based drinks, fruit juice) ritual fluids and ORS, drops or syrups (vitamins, minerals and medicines).
- **Complementary food:** Hygienically prepared home-made mashed food given to an infant after six months of age when breastfeeding alone is likely to be inadequate for his nutritional needs.
- **Bottle feeding:** Use of bottle and nipple/teat for milk, water or juice administration to the infant.

ANATOMICAL ASPECTS OF LACTATION

Milk is produced in the sac-like spaces, alveoli, of the glandular tissue of breast. From alveoli, about 20 small ducts carry milk to their own dilated ends, lactiferous sinuses, which lie under the areola and store milk. From these sinuses, milk passes on to the nipple for supply to the infant. However, it is important for the infant to suckle the

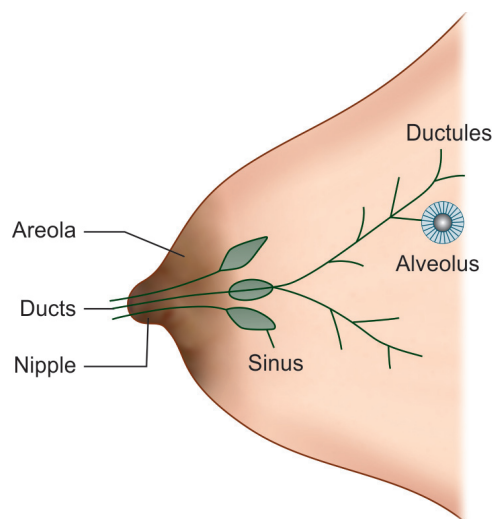


Fig. 12.1: Anatomy of breast.

nipple before milk gets drawn out of the sinuses and the nipple (Fig. 12.1).

PHYSIOLOGY OF LACTATION

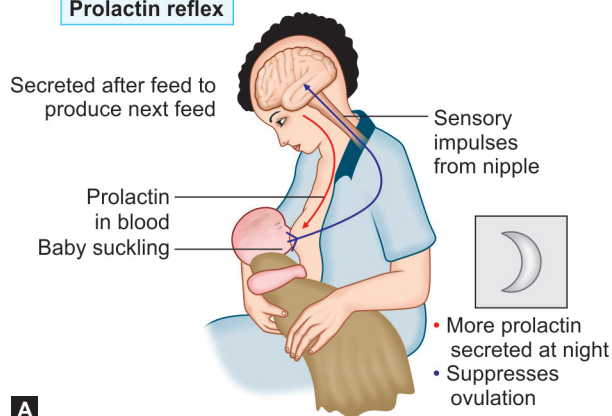
In Relation to Mother

- **Prolactin milk secreting reflex:** Suckling* by baby at breast stimulates alveolar cells of the breast to secrete milk through secretion of the hormone, prolactin, by the anterior pituitary (Fig. 12.2A). Prolactin level reaches the peak around 30 minutes of initiation of breastfeeding, thereby getting the milk ready for the next feed. Since pituitary gland secretes more prolactin during night, breastfeeding at night specially helps to keep good supply of milk.
- **Oxytocin milk ejection reflex:** Suckling by the baby sends sensory impulses from the nipple to the posterior pituitary gland (Fig. 12.2B). The hormone, oxytocin, secreted by the gland reaches through blood to the breast, making the muscle cells around the alveolar cells contract. Thus, milk, which has collected in the alveoli, flows along the ducts to the lactiferous sinuses.

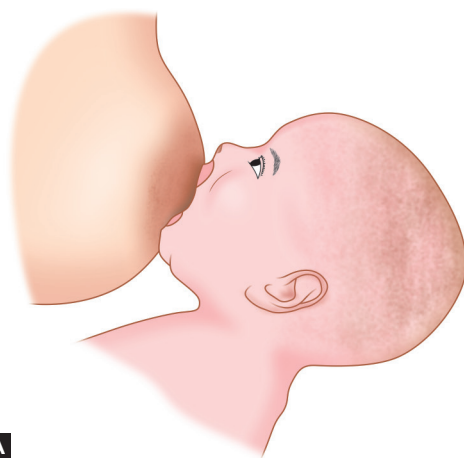
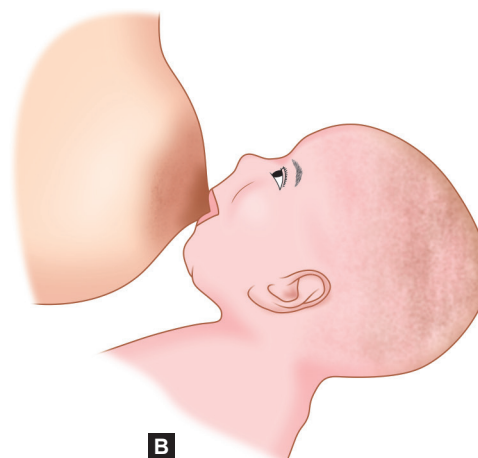
In Relation to the Infant

- **Rooting reflex,** guides the infant to reach the nipple and to have his mouth properly attached to the breast. A good attachment (termed **latching**) with nipple and enough of areola into infant's mouth is essential for effective suckling (Figs 12.3A and B).

* In relation to breastfeeding, "suckling" is a more appropriate term than "sucking".

Prolactin reflex**A****Oxytocin reflex****B**

Figs 12.2A and B: Secreting and ejection milk reflex. (A) Prolactin secreting reflex; (B) Oxytocin ejection reflex.

**A****B**

Figs 12.3A and B: Breastfeeding. Infant's proper attachment (latching) with infant's wide open mouth, everted lower lip, maximum areola in his mouth, and his chin touching the breast is crucial for success of breastfeeding. Note the correct attachment on left. Incorrect attachment on right is in the form of only nipple in infant's narrowly-open mouth with lower lip not turned outward and chin not touching the breast.

- **Suckling reflex**, helps the infant to draw out milk from mother's breast. It consists of drawing the nipple and areola into the mouth, compressing it between jaw-tongue and palate and then drawing out milk by peristaltic movements of the tongue.
- **Swallowing reflex**, helps the baby to swallow milk when mouth is full of it (after one to three suckles). He takes the breath after swallowing. It takes about a second or so for the suckle-swallow-breathe cycle.

BREASTFEEDING/HUMAN MILK: THE SUPREME GIFT

Human milk is decidedly superior to other milks. It is remarkably adapted to the requirements of the infant and provides the best start in life. Exclusive breastfeeding, therefore, deserves encouragement at least for first 6 months and preferably for upto 2 years. When the mother is not able to supply enough of proteins from outside, she should be encouraged to continue breastfeed even longer.

According to a World Health Organization (WHO)/United Nations Children Emergency Fund (UNICEF) document, at least one million deaths per year from diarrhea and infections are absolutely preventable through breastfeeding.

Composition

Table 12.1 summarizes the salient features of its composition in comparison with those of cow and buffalo milk.

Table 12.1: Composition of human, cow and buffalo milk

Components	Human milk	Cow milk	Buffalo milk
Proteins (%)	1.2	3.5	4.2
Fat (g%)	3.8	3.7	8.0
Calories/100 ml	66	66	80–120
Water (%)	88	87	83
Lactose (%)	7.0	4.5	4.8
Iron (mg%)	0.05	0.04	0.2
Vitamin A (IU/100 mL)	170–670	140–280	80
Vitamin C (mg%)	2–6	1–4	1–4
Vitamin D (IU/100 mL)	2.2	1.4	–
Vitamin K (µg/100 mL)	1.5	6.0	–
Calcium (mg%)	35	11.5	–
Phosphorus (mg%)	15	9.0	–
Zinc (mg%)	0.12	0.4	–

Abbreviation: IU, international unit.

Table 12.2: Comparison of foremilk and hind milk

Feature	Foremilk	Hind milk
Timeline	At outset of feed	At tailend of feed
Appearance	Watery	
Highlights of composition	Rich in proteins, lactose, vitamins, minerals and water	Rich in fat
Role/function	In addition to meeting requirements of nutrients, it satisfies infant's thirst.	In addition to meeting infant's nutrition requirements, it supplies more energy.

Composition of foremilk (milk secreted at the outset of a feed) is somewhat different as compared to the hind milk (milk secreted towards the fag end of a feed) as shown in Table 12.2. In short, hind milk is relatively richer in fats which contribute to energy. Hence, both fore milk and hind milk are important for infant's growth and development. The mother should, therefore facilitate infant emptying one breast fully before shifting over to the other breast.

Composition of colostrum (milk secreted in first 3–4 days of birth), transitional milk (milk secreted between 3–4th day and 14th day) and mature milk (milk secreted after two weeks) too differs (Table 12.3).

Composition of milk secreted by a mother who delivers less than 37 week of gestation (the so-called **preterm milk**) is suited to provide more nutrition to the preterm infant to meet his needs for catch-up growth (Table 12.4).

Advantages/Benefits of Human Milk

For the Infant

- **Tailor-made composition:** Human milk has a composition that is ideally tailored to the requirements of a small infant.
- **Readymade:** No preparation needed. It is always fresh, pure and readymade, requiring no preparations. It is at the right temperature. It is uncontaminated and aseptic. It is perhaps because of this factor also that incidence of respiratory and gastrointestinal infections in breastfed infants is far less than that reported in bottlefed babies.
- **Protection against allergy:** Breast milk is non-allergenic. Breastfed babies have seven times less chances of an allergy.
- **Immunoprotection (Box 12.1):** Human milk protects against certain diseases. Its secretory IgA provides protection against respiratory and gastrointestinal infections. It contains lactoferrin, a substance that

inhibits growth of *Escherichia coli*, a common cause of infantile gastroenteritis. Also, it assists in gradually establishing the organism, *Lactobacillus bifidus*, in the baby's intestine. This organism is of help in digestion of sugar. Furthermore, it contains agents against *Staphylococcus* group of organisms which are responsible for septicemia of the newborn.

- **Bonding:** Breastfeeding establishes healthy mother-child relationship. This is due to the psychophysiological interaction that occurs during the act of feeding. The mother derives much satisfaction and a sense of fulfillment from nursing her baby successfully.
- **Prevention of adult diseases:** Human milk possibly prevents arteriosclerotic disease later in life.
- **Protection against ulcerative colitis:** It has now been demonstrated by several investigations that adults who had breastfeeding as infant suffer much less from ulcerative colitis than others.
- **Miscellaneous:** Hypernatremic dehydration which may prove disastrous to an infant's brain seldom occurs in breastfed babies. Evidence has also pooled up, suggesting that incidence of obesity in breastfed babies is far less. Also breastfed infants stand less chance of suffering from neonatal seizures, dental caries and sudden infant death syndrome (SIDS).

For the Mother

- Breastfeeding helps in spacing children since chance of conception in a lactating mother are less, provided her periods have not resumed.
- Breastfeeding also helps in slimming by enabling uterus to return to normal size and also drains away extra fat accumulated during pregnancy.
- Incidence of breast cancer in such mothers is relatively very little.

For the Community

- It is inexpensive, costing virtually nothing and thus economical for individual family, community and the nation.
- It promotes family planning.
- It contributes to reduction in infant morbidity and mortality.

Breastfeeding Schedule

- **Exclusive breast milk:** Breastfeeding should be started within first half to one hour after birth and continued exclusively up to the age of six months.

Table 12.3: Comparison of colostrum, transitional milk and mature milk

Feature	Colostrum	Transitional milk	Mature milk
Timeline	First 3–4 days of birth	4–10 to 14th day of birth	15th day of birth
Appearance	Thick, yellowish	Thin, light yellowish	Quite thin
Composition	Rich in protein, immunoglobulins (IgA, IgG, IgM), antibodies, anti-infective agents (lactoferrin, lactozyme, complement, etc.), fat-soluble vitamins (A, D, E) and K, growth factors; less fat	Rich in fat, protein, lactose, vitamins, energy and water	Rich in fat, protein, lactose, vitamins, energy water
Role/function	Defense against infections	Adequate energy	All nutrients

Table 12.4: Comparison of mature milk and preterm milk

Feature	Mature milk	Preterm milk
Timeline	14th days of birth onwards	Soon after birth
Appearance	Thin	Thin
Composition	Rich in fat, protein, lactose and vitamins, energy, water	Richer in fat, protein, immunoglobulins, lactoferrin
Role/function	Meets need of all requisite nutrients	Supplies extra energy for the catch-up growth

Box 12.1**Protective immunoglobulins, growth factors and enzymes in mother's milk****Protective factors**

- **Secretory IgA:** Protection against respiratory and gastrointestinal infections.
- **Macrophages:** Detecting, engulfing and destroying pathogens and apoptotic cells.
- **Lactoferrin:** An essential growth factor in B cell and T cell, Bacteriostatic against such pathogens as need iron for the growth, i.e. *Escherichia coli*.
- **Lysozyme:** A basic polypeptide, it is instrumental to the immunological system. It has antibacterial action (bacteriostatic) in the gastrointestinal tract, especially against Gram-positive bacteria.
- **Bifidus factor:** Colonization of *Lactobacillus bifidus* which helps in digestion.
- **Complement:** Complementary role to other immunological and non-immunological protective mechanisms.
- **Interferon:** Protection against respiratory viruses (especially influenza virus) by activating innate antiviral mechanisms in the host.
- **Low PABA level:** Protection against malaria.
- **Peroxidases:** Kills bacteria.

Growth factors:

Epidermal growth factor.

Enzymes

- **Lipases:** Lysis of *Entamoeba histolytica* and *Lambliia giardia*; breakdown of milk fat, rendering free fatty acids available before digestion in gut.
- **Amylase:** Digestion of polysaccharides. Available in breast milk after the infant is six months old.
- **Spermine, spermidine and putrescine:** Polyamines in cell growth and differentiation.

Abbreviations: PABA, para-aminobenzoic acid; IgA, immunoglobulin A.

- Breastfeeding should be initiated as early as possible, preferably within half an hour to one hour of birth. It should be exclusive (no other food or water be given) up to six months of age when complementary foods need to be gradually introduced.
- Feeding should preferably be given on a cue. Feeding on cue has now replaced the feeding on demand. Early feeding cues are:
 - Sucking movements
 - Sucking sounds
 - Soft cooing or sighing sounds
 - Hand-to-mouth movements
 - Lip smacking
 - Rapid eye movements
 - Restlessness.

Crying, a late feeding cue may interfere with feeding. Hence feeding need to be given much before that, i.e. on an early cue.

- Cues do point out that the baby is hungry and needs feeding. He should be satisfied at the end of nursing session.
- Breastfeeding should be given at least 8–10 times in 24 hours till lactation is established (1–2 weeks).
- The adequacy of milk supply 1–2 weeks after birth is indicated by:
 - The infant urinates 6–7 times/24 hours.
 - He gains weight satisfactorily, i.e. around 25–30 g daily in first three months. A weight gain less than 500 g every month during first three months needs a check-up.
 - He sleeps for 2–4 hours after the feed.

The so-called **test-feed** involves weighing the baby before and after the mother has nursed him. Its negative points are:

- **Not quite satisfactory:** It is not a very satisfactory method of assessing the adequacy of milk supply.
- **Anxiety-prone:** It may start worrying the mother in case of gains which she thinks are less than what she expects. This may cause undue anxiety to her, thus further reducing the letdown reflex and the milk supply.

Breastfeeding Technique**Proper Positioning**

The mother and the baby should be comfortable and relaxed at the feeding time. Correct position consists in supporting infant's whole body so that it faces the mother and the infant's head, neck and body are in the same plane, and his abdomen touches mother's abdomen (Box 12.2).

Proper Attachment

Good attachment (latching) of infant's mouth on mother's areola and nipple (Fig. 12.3) is important for good suckling. It is indicated by four essentials (Box 12.3).

■ **Improper attachment may cause:**

- Sore nipple
- Incomplete emptying of breast (engorgement)
- Inadequate weight gain.

Box 12.2**Essentials in proper positioning of infant during breastfeeding**

- Infant's head and body should be straight.
- Infant should face the breast in such a way that his nose is just opposite to mother's nipple.
- Infant's body should be close to mother's body, i.e. infant's abdomen should touch mother's abdomen.
- Infant's whole body should be fully supported.

Box 12.3**Essentials of proper attachment**

- Infant's mouth wide open
- Infant's lower lip turned outward
- Infant's chin touching mother's breast
- Most of areola inside infant's mouth.

- **Factors causing improper attachment include:**
 - Inverted nipple
 - Ignorance of technique
 - Poor guidance
 - Exposure to prelacteal feeds and artificial feeding (nipple confusion).

Basic Principles of Breastfeeding

- **No prelacteal feeds:** As a rule of the thumb, no prelacteal feeds (not even honey or the so-called *gutti*) should be given to the neonate. Prelacteal feeds are known to:
 - Enhance risk of infections
 - Decrease suckling, stimulation and milk production
 - Contribute to poor attachment
 - Interfere with establishing breastfeeding
 - Cause engorgement of breasts.
- **Exclusive breast milk:** Breastfeeding should be started within first half-one hour after birth and continued exclusively up to the age of six months.
 - During these six months, the infant should not be given any juice or water. Multivitamin drops and medicines, if warranted, are allowed.
 - There is now sufficient evidence that exclusive breastfeeding can maintain hydration, urine output, urinary specific gravity and rectal temperature without water supplementation even at environmental temperatures varying from 23–41°C and relative humidity from 15–96%.
 - On the other hand, early supplementation may lead to infection, lactation failure and dilution of beneficial effects of breastfeeding.
- **Complementary feeds:** After six months, breastfeeding plus complementary feeding need to be continued upto two years.
- **Hygiene:** Breastfeeding should be done in a clean and safe manner as possible.
- **Art of feeding:** Mother should be well conversant with “how to put the baby to breast” and “how to remove him off it”.
- **One breast at a time:** At least one breast should be completely emptied at every, sitting. Shifting to other breast should be after the first breast is completely emptied.
- **Nursing time:** Starting from the initial five minutes, the nursing time can be gradually increased to 15–20 minutes in the subsequent days.
- **Burping:** In order to **kick out** the swallowed air, the act of nursing should be followed by burping. It consists of holding the baby erect over mother’s shoulder or making him sit in mother’s lap and then patting or rubbing his back so that he eructates the swallowed air. Failure to do so may cause regurgitation, vomiting, and even abdominal pain.
- **Mother’s diet:** Mother should give adequate attention to her diet, personal hygiene and health and should have sufficient rest. As far as possible, she should avoid unnecessary use of drugs which may have adverse effects on the baby.

- **Markers of adequate milk supply:** A contented baby is a good guide as regards the adequacy of milk supply. A contented baby—
 - Sleeps well after feed,
 - Is playful, and
 - Passes urine at least six times/day.
 The most reliable criterion of adequate supply of breast milk and growth of the baby is the weight gain. A baby who gains less than 500 g in any four week period in first three months of life or 200 g in any four weeks period in second three months is likely to be malnourished later.
- **Working woman and expressed breast milk:** In case of a working mother, her **expressed** milk can be spoon-fed to the baby in her absence. The mothers should be conversant with the technique of expressing milk. Using both hands, she should squeeze gently from the base of the breast towards the areola and nipple. Then the breast and areola should be squeezed between fingers and thumbs and the milk is collected in a clean container. The container should be stored in a cool place. If stored outside the refrigerator, it has to be used within 12 hours. Just before feeding, this milk should be warmed by placing the container in a bowl of hot water. Technique of expressing milk is described later in this very chapter.

Contraindications

There is virtually no absolute contraindication, excepting malignancy. Box 12.4 lists situations where breastfeeding may be temporarily avoided.

Common Breastfeeding Problems

Inverted or Retracted Nipples

Since these may cause difficulty in breastfeeding, the mother is advised to manually stimulate, stretch and roll

Box 12.4

Situations warranting temporary avoidance of breastfeeding

In Mother

- Chronic diseases such as active tuberculosis, leprosy, malignancy, beriberi, AIDS, etc. Many authorities advocate continuing breastfeeding in the first two provided chemotherapeutic coverage is being given.
- Mothers stubbornly addicted to alcohol or heavy doses of some drugs. Those on heavy metals, phenobarbital, hydantoin, steroids, etc. should also not be allowed to breastfeed their babies.
- Psychosis.
- Local conditions, e.g. breast abscess, cracked nipples, etc. Breastfeeding must be resumed as soon as possible.

In Infant

- Gross prematurity of the baby or other conditions in which the newborn cannot suckle.
- Inborn errors such as phenylketonuria, galactosemia or lactose intolerance.
- Breast-milk jaundice, provided that serum bilirubin approaches critical level.
- Biological mother may avoid breastfeeding an infant who is to be passed on to another couple.

Abbreviation: AIDS, acquired immunodeficiency syndrome.

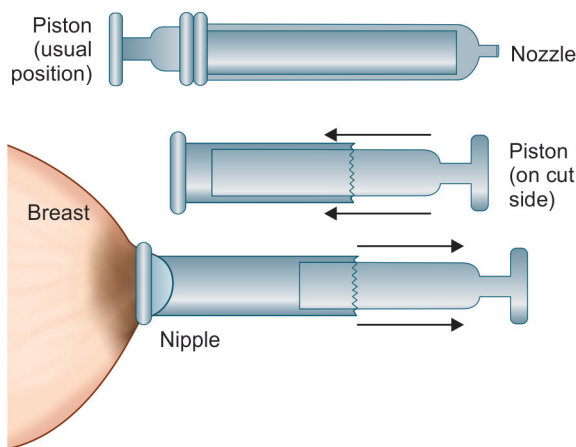


Fig. 12.4: Plastic syringe method for retracted/inverted nipples. Step 1: Cut the nozzle-end of a plastic syringe. Step 2: Introduce the plunger from the cut-end rather than the normal smooth end. Step 3: Guide the mother to attach the smooth end of the syringe over the nipple and then gently pull out the plunger. As a result of negative pressure thus created, the nipple protrudes out. Once suction is released and syringe removed, the infant is allowed to attach on the breast for feeding. The method may need application several times in a day for some days.

out the nipples to make them protractile (prominent) several times a day, especially before offering the feed. In a large majority, the condition resolves in a couple of weeks. Else, the plastic syringe method may be employed (Fig. 12.4).

Sore Nipple

The causes include poor attachment, frequent application of soap, forcibly pulling the infant off the breast while he is still engrossed in sucking, natal tooth and fungal infection of the nipple. Application of hind milk and airing after the feeds resolve the problem.

Breast Engorgement

Swollen, congested and painful breast may result from overdistention of alveoli when adequate emptying of breast does not occur because of delayed or infrequent feeding, faulty attachment or incorrect positioning of the infant at the breast.

Treatment consists in application of warm water packs and oral analgesics. Gentle expression of milk assists in softening the breast. Thereafter, the infant should be put to breast, ensuring correct positioning and attachment.

Breast Abscess

It may result from delayed attention to engorged breast, infected sore or cracked nipple, mastitis or a blocked duct. It may cause high fever in addition to local manifestations. Treatment is incision and drainage along with antibiotics and analgesics.

Not Enough Milk

Though a number of factors (wrong technique/ positioning, infrequent or hurried breastfeeding, local problems of breast, etc.) can cause **not enough milk**; at times mother's impression is not well founded. In such cases, the infant

demonstrates adequate weight gain, passes urine at least six times/day and sleeps for 2–3 hours after each feed. Such mothers need reassurance.

In others, it is important to look for the reason which could be in relation to the:

- **Mother:** Faulty technique, maternal anxiety, painful conditions of breast, introduction of prelacteal feeds/ bottle feeding), or
 - **Infant:** Unwell infant, cleft lip/palate.
- Appropriate corrective action is needed in such instances. Broadly, the mother should be advised:
- Adequate rest
 - Adequate intake of fluids
 - Allowing the infant to feed on each breast on **cue** rather than crying or demand as often and for as long as feasible
 - Facilitating the infant to remain with her.

Not enough milk amounting to lactation failure is described next in this very Chapter.

World Health Organization (WHO)'s 10 Point Strategy for Successful Breastfeeding

1. Have a written breastfeeding policy—routinely communicated to all health staff.
2. Train all health staff in skills to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within half an hour of birth.
5. Show mothers how to breastfeed, and how to maintain lactation even if they should be separated from their infants.
6. Give newborn infants no food or drink other than breast milk, unless medically indicated.
7. Practise rooming in (allow mothers and infants to remain together) 24 hours a day.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers (also called dummies or soothers) to breastfed infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

LACTATION FAILURE

Definition

Lactation failure (LF) is failure on the part of the breasts to produce adequate quantity of milk which manifests as failure to sustain growth in a normal infant within two standard deviations of the standard for the infant in the first six months of age.

- **Complete LF**, means total absence of milk flow or secretion of only a few drops of milk following regular suckling for a period of at least seven days.
- **Partial LF**, means insufficient milk flow by the mother who is otherwise regularly breastfeeding her baby so that the infant needs supplementation by artificial feeding for sustaining growth (Fig. 12.5).

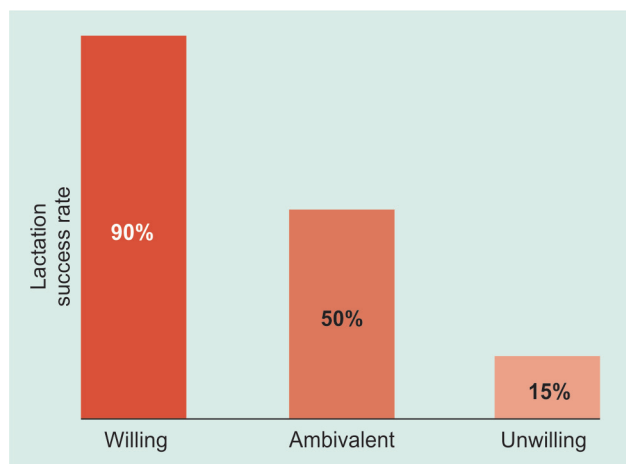


Fig. 12.5: Attitude of the mother has a great bearing on success of lactation.

Box 12.5 Etiology of lactation failure

• Maternal factors

- **Psychosocial:** Lack of motivation/confidence/will, dislike for breastfeeding because of wrong notions, stress and anxiety, rejection of baby, previous unpleasant experience, undue concern for figure, aping the West, influence of advertisements favoring breast milk substitutes.
- **Physical:** Breast conditions, e.g. nipples that are retracted, cracked or sore, painful conditions, e.g. mastitis, engorgement or abscess, malnutrition, sickness, pregnancy, contraceptive pill, alcoholism, smoking and working mother.
- **Infant factors:** Sick infant, prematurity, suckling problem, e.g. cleft palate, nasal block and thrush oral.
- **Feeding factors:** Prelacteal feeds, delayed initiation, poor technique, introduction of bottle.

Etiology

Lactation failure is usually not the cause, but a consequence of a number of factors which are responsible for introduction of top milk under the wrong notion of **not enough milk**, or because of maternal-child separation, working mothers, sore/cracked nipples, etc. (Box 12.5).

The sequence of events in the development of lactation failure is sketched in Figure 12.6. It will be seen that in a vast majority of the cases it is more or less preventable.

Prevention

The most important preventive measures are through antenatal check-up of the breasts, antenatal preparation of the mother for breastfeeding, feeding as early as possible after delivery, remedial measures for anatomical defects in the breasts and complete emptying of the breasts. If necessary, even manual expression of milk following feeds may be done. Most of LF can be prevented if the pediatrician forms a part of the team for the antenatal care, and the breasts of every expectant mother are carefully examined.

Treatment

Metoclopramide and chlorpromazine may help certain mother with lactation failure to revert to normal milk production through their galactagogue effect. Nevertheless, the best galactagogue is the **frequent suckling**.

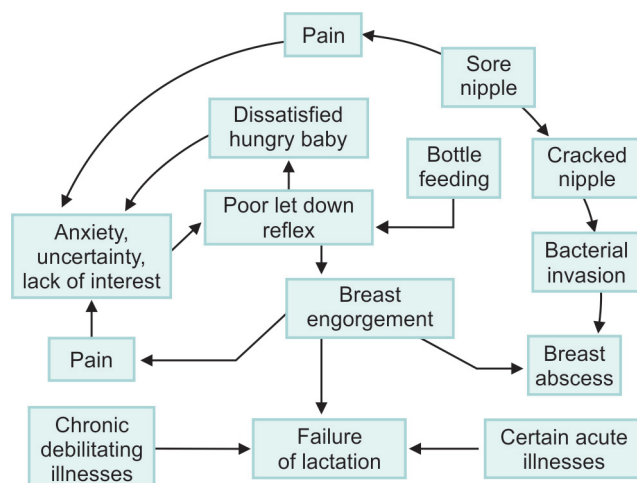


Fig. 12.6: Sequence of events in lactation failure.

Relactation in Partial Lactation Failure

Satisfactory relactation in these mothers is attained by motivation and encouragement. They need to be educated on the supremacy of breast milk and actively involved in achieving success with **commitment for the cause**. As the days pass by, the amount of top feed needs to be reduced in increments until the infant is entirely of mother's milk.

Relactation in Complete Lactation Failure

This is rather more difficult situation. In addition to motivation, encouragement and moral support, the following actions are warranted:

- Nipple stimulation exercises by nipple stroking, massaging the breast and rolling the nipple between thumb and the index finger.
- Frequent suckling, at least 8-10 times a day, each session lasting 10-15 minutes for each breast.
- **Drop and drip method:** It may be employed if the infant fails to suckle for 8-10 minutes. The method consists in expressing some breast milk or top milk in a cup and gradually pouring it over as drops over the breast. As the drops slide over the nipple down into infant's mouth, he is stimulated to suckle at the breast.
- **Nursing supplementor:** The so-called **Lact-aid supplementor**, especially of value in infants having nipple confusion, may be used to induce suckling in the infant on an empty breast (Fig. 12.7). This gadget consists of a fine infant feeding tube. The tube is employed as a drawing straw. It is made to pass from milk in a cup to the infant's mouth. Its end is placed along with mother's nipple so that the baby suckles at both the nipple and the tube simultaneously. As he suckles when milk passes into his mouth, the nipple gets stimulated, thereby enhancing the prolactin reflex which increases the milk production.

Evidence of Successful Relactation

- Appearance of first milk secretion in 2-10 days.
- Partial restoration of breastfeeding with reduction of top feed to half of the initial.



Fig. 12.7: Supplemental (supplementary) suckling technique. Carried out carefully, it may prove a boon for stimulating lactation in complete lactation failure.

- Complete restoration of breastfeeding with total withdrawal of top feed.
- Satisfactory weight gain by the infant.

EXPRESSED BREAST MILK (EBM)

A situation may arise when the mother needs to express her milk which can be fed to the infant subsequently. Though pumps (usually expensive) are available, manual expression comes in hand and should be taught to each mother.

Indications

- For feeding preterm/low birth weight (LBW)/sick baby who is not able to breastfeed.
- For donating as donor milk for benefit of other babies.
- As a part of exclusive breastfeeding by working mothers who can express milk in advance and store it for feeding to the infant.

Prerequisites

Before indulging in the procedure, she should carry on the following prerequisites:

- Wash her hands with soap and water.
- Make herself comfortable.
- Keep a clean container ready.

Steps of Milk Expression

1. Massage the breasts gently towards the nipples.
2. Place the thumb (on top) and index finger (on under-surface opposite thumb) opposite each other just outside the areola (Fig. 12.8A).
3. Compress (press back towards the chest) and then gently squeeze to release milk into the container kept ready under the nipple and areola (Fig. 12.8B).
4. Repeat step 3 in different positions all around the areola.
5. Similarly, express milk from the other breast as well.
6. Ideally, expression of milk needs to be done 8–10 times/24 hours. This assists in maintaining good lactation and safeguarding against engorgement.

Storage

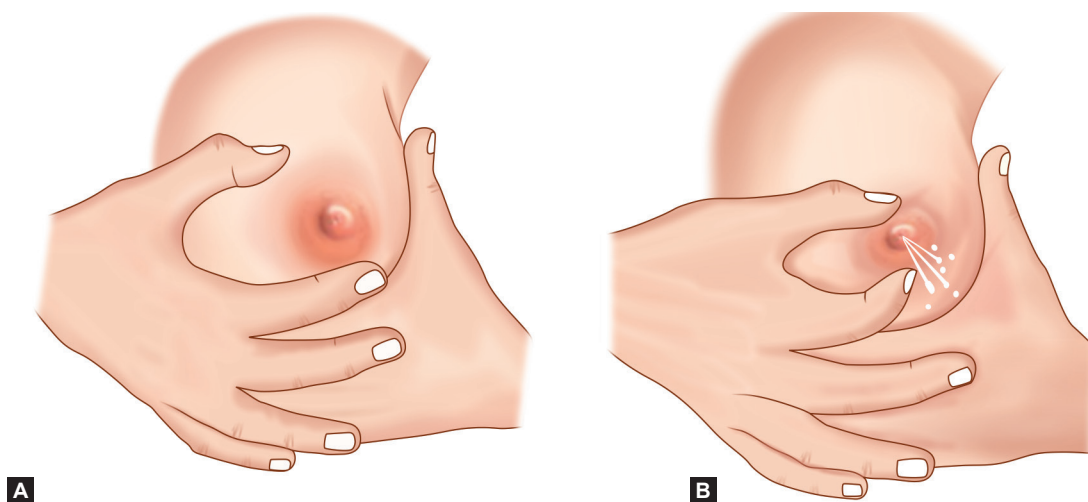
Table 12.5 shows the lifespan of EBM under different conditions of storage.

Feeding of Low Birth Weight Infants

Unlike term neonates, preterm/LBW infants are difficult to feed for multiple reasons. The topic is described in Chapter 17 (Neonatology).

Feeding of HIV-Positive Mothers' Infants

Exclusive breastfeeding is the preferred feeding option for human immunodeficiency virus (HIV) exposed infants less than six months of age. However, if in some women breastfeeding may not be possible for example in situations of maternal death and severe maternal illness.



Figs 12.8A and B: Expressed breast milk—Manual expression. (A) Mother's thumb needs to be above the nipple and areola and her index finger below the areola—just opposite the thumb. Her other fingers support the breast; (B) Breast is pressed between the thumb and index finger (with support from other fingers) behind the areola and nipple. As such or on slight squeezing, milk begins to come. The press and release cycle is repeated all around the areola so that complete emptying occurs.

Table 12.5: Lifespan of expressed breast milk (EBM) under varying storage conditions

Storage	Lifespan
Room temperature	6–8 hours
Fridge	24 hours
Freezer	3 months

In these cases **exclusive replacement feeding** should be done only when AFASS criteria are fulfilled as follows:

- Affordable,
- Feasible,
- Acceptable,
- Sustainable, and
- Safe.

Exclusive breastfeeding should be done for at least six months, after which complementary feeding should be introduced gradually, irrespective of whether the infant is diagnosed HIV negative or positive by early infant diagnosis (EID). For **breastfeeding infants' diagnosed** HIV negative, breastfeeding should be continued until 12 months of age ensuring the mother is on antiretroviral therapy (ART) as soon as possible. Salient recommendations of Indian Academy of Pediatrics (IAP)-improving infant and young child feeding (IYCF) subspecialty chapter are given in Table 12.6.

HUMAN MILK BANKING

Human milk banking (HMB) is an initiative that facilitates provision of milk to neonates whose biological mothers are incapable of doing so. The collection of human milk needs to be from healthy donors who willingly give away their breast milk for the benefit of the needy infants.

This concept has emerged in a big way—in fact, as a movement in the Western countries where such banks are running in accordance with the set guidelines and protocols to ensure safety of the milk. In India and other resource-limited countries, the initiative is still in infancy and largely restricted to Maharashtra and Gujarat.

Concerted efforts by the pediatricians, neonatologists, nursing staff and non-government organizations (NGOs) in promoting the HMB initiative in India shall contribute to survival of a substantial proportion of neonates who otherwise die for nonavailability of human milk.

COMPLEMENTARY FEEDING

The term weaning means to **be taken off the breasts or introduction of top feed**. The latter meaning is more relevant in infant nutrition. Though in vogue for several decades, the weaning is an inappropriate terminology. The better and currently recommended terminology is complementary feeding.

Table 12.6: Salient recommendations for feeding of infants of human immunodeficiency virus (HIV) positive mothers

Mother and infant's HIV status	Recommendation
Mothers known to be infected with HIV; infants are HIV uninfected or of unknown HIV status	<ul style="list-style-type: none"> • Exclusive breastfeeding for the first six months of life, introducing appropriate complementary foods thereafter, and continuing breastfeeding as long as possible. • Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided. • Initiate maternal ART and give NVP for six weeks.
Infants of mothers who are receiving ART and are breastfeeding	<ul style="list-style-type: none"> • Six weeks of infant prophylaxis with daily NVP. • If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP (or twice-daily AZT). • Infant prophylaxis should begin at birth or when HIV exposure is recognized postpartum.
Mother diagnosed with HIV during labor or immediately postpartum and plans to breastfeed	Along with maternal ART, extended NVP prophylaxis to infants for 12 weeks.
Mother diagnosed with HIV during labor or immediately postpartum and plans ERF.	<ul style="list-style-type: none"> • Refer mother for HIV care and evaluation for treatment. • Give infant NVP prophylaxis to six weeks.
Infant identified as HIV exposed after birth (through infant (at six weeks or after) or maternal HIV antibody testing) and is breastfeeding	<ul style="list-style-type: none"> • Initiate maternal ART and give to the infant NVP prophylaxis. • Perform infant DNA/PCR test if he is six weeks old or older; immediately initiate six weeks or longer of NVP—strongly consider extending this to 12 weeks.
Infant identified as HIV exposed after birth (through infant or maternal HIV antibody testing) and is not breastfeeding	<ul style="list-style-type: none"> • Refer mother to ART Centre after CD4 tests and baseline test and treatment. No NVP (No drugs) is to be started. • Do HIV DNA/PCR test in accordance with national recommendations on early infant diagnosis; no infant ARV prophylaxis; initiate treatment if the infant is infected.
Mother receiving ART, but interrupts ART regimen while breastfeeding (such as toxicity, stock-outs or refusal to continue). Maternal ART is restarted or until one week after breastfeeding has ended	<ul style="list-style-type: none"> • Determine an alternative ART regimen or solution; counsel regarding continuing ART without interruption. • NVP is given until six weeks after.

Abbreviations: HIV, human immunodeficiency virus; ART, anti-retroviral therapy; ERF exclusive replacement feeding; NVP, nevirapine; DNA-PCR, deoxy ribonucleic acid—polymerase chain reaction; ARV, antiretroviral; AZT, azidothymidine.

192 Definition

By definition, complementary feeding means “*introduction of nutritious foods over and above breastfeeding after six months of age when breast milk becomes insufficient to meet infant’s needs*”.

These energy-dense foods should be:

- Cost-effective
- Affordable
- Easily available
- Well-tolerated.

Recommended Age

Just after completion of 6 months of age is the most appropriate time for introducing complementary foods. The whole process should be gradually completed by 9 months–1 year of age when the child should be taking almost the adult diet.

Whereas delayed introduction of complementary foods is known to cause malnutrition and growth retardation, premature introduction of such foods exposes the infant to the risk of infections and the resultant morbidity and mortality. Besides infections, too early introduction of complimentary feeds, including cow milk, or buffalo milk has other problems (Box 12.6) and is not recommended except under special circumstances such as when the mother is not able to produce sufficient milk despite the best of efforts.

Prerequisites/Attributes of an Ideal Complimentary Food

- **Homemade, available:** These foods are fresh, easily available, economical and provide exposure to variety. Homemade, readymade foods, e.g. biscuits, bread, pastry, etc. come in handy at odd times.
- **Fresh and hygienic:** Food must be freshly and hygienically prepared, avoiding prolonged storage.
- **Palatable:** Soft, easy to eat and tasty.
- **Cost-effective/affordable:** The foods should be in keeping with the socioeconomic status of the family.
- **Culturally acceptable:** It is preferable to employ available food and culturally acceptable foods normally taken by the family with appropriate modification.
- **Energy dense:** Food can be made energy dense by adding oils and fat. In addition, such an addition

Box 12.6

Problems associated with too early initiation of complementary feeds

Short-term

- Decreased suckling frequency and intensity, leading to decreased milk production.
- Iron deficiency unless cereal preparations used are rich in iron.
- Hypernatremia
- Weaning diarrhea.

Long-term

- Malnutrition in the poor
- Obesity in the affluent
- Hypertension
- Arteriosclerosis.

Box 12.7

Types of complementary foods used by the community

Appropriate (first line) weaning food

Fresh homemade, locally available, culturally acceptable, hygienically prepared, energy dense and cost-effective foods like:

- Combination of cereals and pulses (khichadi, dal-rice etc.), porridge, suji, dalia, kheer, khaman dhokla, idli, dosa, ragi, rice preparations etc. in any form fortified with sugar and oil or fried.
- Mashed banana, sweet potato and potato.
- Milk added to cereals preparations.
- Sprouted legumes, nuts, dry fruits etc. depending upon the affordability.

Acceptable (second line) weaning foods

These include home available foods like:

- Breads, cakes, pastry, biscuits, cheese and icecream etc.
- Caloric dense fruits, etc.

Avoidable (third line) weaning foods

- Commercially available artificial foods or tinned foods.
- Fast food or junk food.
- Low caloric fruits juices and soups.
- Repeatedly fry foods containing trans fatty acids (which predispose to obesity, atherosclerosis, cardiac and neurological problems in future life).

increases palatability of food, provides essential fatty acids and enhances absorption of some vitamins and micronutrients. Amylase-rich foods can be prepared by germinating cereal flours. Sprouting increases the vitamin B content. Malting increases the digestibility and vitamin (riboflavin and niacin) and iron content.

Types of Complementary Foods

The complementary foods can be divided into different groups (**3 “A”s**) based on their availability and nutritional advantages (Box 12.7).

Complementary Feeding Regimen

- To begin with, one of the foods like mashed ripe banana, mashed potato, cereal, curd, pulses, khichri and dalia, etc. should be introduced in the form of a soft porridge when the child is just beyond six months of age.
- The food should be given in small amounts (say 2–3 table spoonful). The amount can be built up slowly. Likewise, frequency too is increased from twice a day to 3–4 times a day by the fag end of the first year.
- Every 1 or 2 weeks, a new food may be added.
- If the child does not like a particular food, this may be omitted for the time being. A one-year-old should be taking the family food which, if need be may be mashed or chopped.
- Germinated cereal flour or pulse flour is an amylase rich food (ARF) and is able to dramatically reduce the viscosity of high dietary porridges. It makes an excellent weaning food.
- Fish, egg, meat, etc. should be introduced later in view of the possible risk of allergy to proteins. In case of egg, begin with the yolk.
- Addition of animal protein makes up for the deficiency of limiting amino acid, methionine, which may be seen in

Box 12.8 Four food groups recommended for a one-year-old and toddler's daily dietary intake

1. Milk and dairy items such as curd
2. Cereals-pulses complex
3. Vegetable-fruit complex
4. Nonvegetarian foods—eggs, fish, chicken, meat.

infants exclusively on a staple cereal and a legume. Staple cereal as such is deficient in lysine, but this deficiency is made up when legumes are consumed concurrently.

Box 12.8 lists the four food items that should be essentially included in a toddler's daily dietary intake for appropriate growth and development.

ARTIFICIAL (FORMULA) FEEDING

As already pointed out, only a very small proportion of infants really require artificial feeding. The existing factual position is, however, quite different. Despite the acknowledged superiority of human milk, today artificial feeding, especially in the form of bottle feeding, has come to stay. The worse it has, in actual fact, considerably increased with rapid industrialization.

The situation is understandable as regards the urban elite who regard breastfeeding as time consuming, messy, an encroachment on activities and so on the so forth. They find the readymade milks simple, convenient and a sort of boon to their personal freedom.

The more disturbing fact is that even the urban poor and the rural women who can hardly afford the luxury of expensive artificial feed, have now been influenced by this trend. Whereas the former are mostly influenced by the tempting publicity of the manufacturers as also by the personal and social considerations, the village folks merely ape the urban trend.

Let us remember that artificial feeding is an expensive affair. Imagine a baby of just four months of age needing almost 2.5 kg of milk powder every month and even more in the subsequent months.

What is more bothersome is that artificial feeding means exposure to hazards such as underfeeding and multiple nutritional deficiencies from over dilution of the formula, gastroenteritis and other superadded infections.

Long-term sequela of artificial feeding include:

- Lactose intolerance
- Obesity
- Atherosclerosis
- Relatively poor learning abilities
- Family breakup and
- Population explosion.

COMMON FEEDING PROBLEMS

Most infants, particularly newborns, suffer from such feeding problems as regurgitation, vomiting, suckling and swallowing difficulties, dehydration, fever, excessive crying, three months colic, change in bowel habit, underfeeding, overfeeding or bottle addiction. All these are preventable.

Too little feed, too heavy feed, too frequent feed, wrong feeding technique, poor respect to bottle hygiene, etc. figure prominently among the underlying causes.

Regurgitation

Several babies (not breastfed) spit up a little of the feed along with swallowed air. **Possetting** is the name given to this phenomenon. With some babies, possetting becomes a habit. They relish to bring back some milk and chew it just like a cow chews the cud. This is called **rumination**. Though harmless, it does make the baby somewhat smelly. In order that he does not inhale any bit of the regurgitated milk, he should be put on his side and never on his back. This position also makes it difficult for him to regurgitate and continue with rumination.

Regurgitation need not bother unless it is interfering with the nutrition of the baby. Also, if the baby brings back the entire food, particularly more than once, there is a case for finding out the cause.

There is a notion that regurgitation is because of wind production. It is not that the baby is a small wind-producing machine, but because he has swallowed excess air with feed or as a result of crying. The solution lies in guiding the mother about the proper technique of burping.

Vomiting

It may be due to overfeeding, prolonged burping, too much of swallowed air, gastroenteritis or some other infection. If the baby shoots the milk half way across the room, the so-called **projectile vomiting**, the possibility of hypertrophic pyloric stenosis exists.

Suckling and Swallowing Difficulties

Some difficulty in suckling is normal during the first few days. It is understandable since this is the period in which the baby and the mother are practicing the technique.

Certain mechanical problems such as cleft palate, cleft lip, large tongue and nasopharyngeal obstructions as in choanal atresia, may interfere with feeding. Local conditions of the breast like cracked nipple, retracted nipple, engorgement and abscess also cause sucking difficulties.

Preterm baby is prone to have suckling and swallowing difficulties. Likewise, cardiac or respiratory disease associated with tachypnea, intracranial hemorrhage and neonatal jaundice figure among several causes of feeding difficulties.

Dehydration and Fever

Disinclination to feed, fever and drowsiness may occur in some newborns about the third or fourth day of life. In such infants, one should exclude infections (not forgetting urinary tract infection) as the cause of dehydration fever.

The baby with dehydration fever may lose 5–15% of body water. Administration of additional feeds of water over about 12 hours brings down the temperature. Simultaneously, he begins to accept feed normally and gains weight.

If a fulminant infection is seriously suspected in an infant who is immature or is at risk for one or the other reason, antibiotics are recommended even if a specific site of infection cannot be recognized.

194 Excessive Crying

Crying in a newborn is almost always a manifestation of hunger or thirst, chilliness, need for the mother or a wet napkin. Repeated crying may begin to get on the mother's nerves. An insecure mother may not develop the much-needed warm emotional relationship with such a baby. There are, at times, instances of baby-battering.

Irritability of an infant during the mother's menstrual periods is well-known observation. Whether it is related to fall in the breast milk supply, mother's irritability or some substances in breast milk during menstruation that cause discomfort to the infant is not clear.

Colic

Sometimes a baby begins crying soon after birth, particularly towards late afternoon or evening and keeps doing so during the first three months or so. This condition has been christened three months colic, or evening colic. None of the above mentioned causes seems to account for its occurrence. Excessive intestinal activity is said to be the cause. It is borne out by the presence of exaggerated bowel sounds as revealed by auscultation. Administration of a mild antispasmodic agent may help these infants.

Change in Bowel Habit

Infants on cow milk, especially if underfed and given inadequate fluids and sugar may pass constipated stools, i.e. stools of hard consistency,—which cause a good deal of straining and discomfort. As a result, the fear of pain may cause retention. The passage of such a stool, on its own or following rectal examination, can lead to anal crack or fissure. Some infants start having spurious diarrhea.

- Most constipated newborns respond to addition of water, some brown sugar and glucose to the intake.
- In obstinate constipation, one should exclude cretinism and congenital megacolon (Hirschsprung disease).
- Recurrent episodes of loose motions are often due to poor bottle hygiene.

Underfeeding

A highly diluted formula, often due to ignorance or economic considerations, is a well-known cause of failure to gain weight. The underfed baby takes his feed quickly, showing that he has been hungry for long. Dissatisfied with the amount made available to him, he usually cries and cries until he goes to sleep. After a few hours, usually much before the due time for feed, he wakes up and cries.

Bottle Addiction

It is not infrequent to see mothers grumbling that "*the little rascal refuses to part with the bottle*" even at 24 months. Little do they realize that the reason is indeed rooted in their failure to have replaced the bottle by spoon and cup at about 6 months or little earlier. It is unwise to have a baby on bottle after 1 year of age.

Overfeeding

It is not a common problem in our country. Most infants, as a rule, refuse to accept excess feed and pushing the feed forcibly is quite a difficult job. But, then, some mothers do manage to give the baby larger and larger feeds. These babies are likely to suffer from infantile obesity. That does not, however, always happen. Some just stop gaining weight. Such a baby is unhappy, vomits large amount of feed, has fatty diarrhea and keeps crying.

Inexperienced Mothers

Not all mothers are good enough and well prepared for the newborn. Some are sadly lacking in self-confidence and unsure how to handle the baby. They worry too much and are very apprehensive. Their nervousness somehow influences the baby. As a result, he becomes more demanding and cries a lot to the mothers' further annoyance. This interaction may lead to rather unhealthy relationship between the mother and the baby.

We have observed such a situation very often in the case of young educated mothers who opt to live by one or to the other stereotyped handbook of baby care. They just try to blindly ape it rather than follow sound advice and their own judgment based on individual merits of the situation.

Multiple Choice Questions

1. Whey-casein ratio in mother's milk is:
 - A. 50:50
 - B. 80:20
 - C. 60:40
 - D. 70:30
2. Hind milk is rich in:
 - A. Fats
 - B. Protein
 - C. Micronutrients
 - D. Water

contd...

3. Colostrum is rich in:
 - A. Proteins
 - B. Mineral
 - C. Immunoglobulins
 - D. All of the above
4. Compared to mature milk, preterm milk is richer in:
 - A. Protein
 - B. Zinc
 - C. Sodium
 - D. All of the above
5. The neuroendocrine reflex, "let-down reflex", is mediated by:
 - A. Oxytocin
 - B. Prolactin
 - C. Estriol
 - D. Placental lactogen
6. Spot the antiemetic that has lactagogue effect:
 - A. Domperidone
 - B. Metoclopramide
 - C. Promethazine
 - D. Ondansetron
7. Components of good attachment include:
 - A. Most of the areola in baby's mouth
 - B. Baby's lower lip everted
 - C. Baby's chin touching the mother's breast
 - D. All of the above
8. Adverse effects of bottle feeding include each of the following, except:
 - A. Superimposed infections
 - B. Bottle-baby disease
 - C. Late hemorrhagic disease of the newborn
 - D. Eczema

Answers

- | | | | | | |
|------|------|------|------|------|------|
| 1. B | 2. A | 3. D | 4. D | 5. A | 6. B |
| 7. D | 8. C | | | | |

Clinical Problem-solving**Review 1**

This 3-day-old baby girl's 22-year-old mother has a problem. She has inverted nipples that are a roadblock in proper attachment of neonate's mouth to the nipple.

1. What should be the first line of action to resolve this problem?
2. If the first line of action does not work, what should be the advice?
3. Could this problem be sorted out during obstetrical checkups antenatally?

Review 2

A 25-year-old mother, known to be infected with HIV but not on any ART, reports to a pediatric OPD with a 2 weeks infant weighing 2.5 kg suffering from upper respiratory infection. The infant's HIV status is unknown.

1. How will you treat infant's upper respiratory infection?
2. Do this mother and infant need ART?
3. What about breastfeeding and complementary feeding?

Answers**Review 1**

1. The mother should manually stimulate, stretch and roll out the nipples to make them prominent several times a day, especially before offering the feed. In a large majority, the condition resolves in a couple of weeks.
2. If the condition fails to resolve in a couple of weeks, the plastic syringe method may be employed.

3. Hoffman technique consists in placing the thumbs at the right and left edges of the areola. While pressing inward slightly, the thumbs are pulled firmly apart. This maneuver is repeated at least four times and then again with the thumbs at the top and bottom of the areola.
Breast shells, worn prenatally, assist in solving the problem of flat or inverted nipples.

Review 2

1. This infant should receive usual therapy for URTI, i.e decongestant therapy as is routinely given to children.
2. Of course, the mother must be initiated on appropriate ART as soon as possible. The infant should also be administered NVP for a minimum of 6 weeks.
3. Current recommendations are exclusive breastfeeding for the first six months of life, appropriate complementary foods thereafter and continuing breastfeeding as long as possible.
Once a nutritionally adequate and safe diet without breast milk can be provided, breastfeeding may be discontinued.

FURTHER READING

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OVERVIEW

According to the World Health Organization (WHO), malnutrition is a **global problem**, having adverse effects on the survival, health performance and progress of population groups. The effects are of the highest order in the resource-limited countries such as India.

In India, over the recent decades, the incidence of severe malnutrition as also low birth weight (LBW) infants has gradually fallen though only to an unsatisfactory level. According to the National Family Health Survey-3 (NFHS-3), mild to moderate malnutrition which eventually ends up in stunted growth continues to exist in around 48% of the pediatric population. These substandard survivors are likely to suffer from consequences such as poor quality of life (QoL), low cognitive development and learning skills over and above other handicaps.

Considerable morbidity and (at times mortality) accompanies nutritional anemias and other micronutrient and vitamin deficiencies, directly or indirectly.

CERTAIN DEFINITIONS

- The term, **protein energy malnutrition (PEM)** implies undernutrition predominantly of energy and protein.
 - **Undernutrition** means a state of poor nutritional status as a result of inadequate intake, malabsorption or excessive loss of nutrients.
 - **Overnutrition** denotes excessive intake of nutrients as in exogenous obesity.
- The term, malnutrition has under its umbrella both undernutrition and overnutrition.
- **Underweight** means low weight for age; it is a combined indicator of both acute and chronic undernutrition.
 - **Wasting** indicates low weight for height as a consequence of recent/acute undernutrition.
 - **Stunting** means low height for age. It is an indicator of chronic undernutrition.

PREVALENCE

South Asia (India, Pakistan, Bangladesh, and Nepal) is known for the highest prevalence of underweight children. In India, prevalence of undernutrition, as per 1998–1999 and 2005–2006 NFHS, is shown in Table 13.1. Prevalence of undernutrition is higher in rural than in urban population.

ECOLOGICAL OF MALNUTRITION

Ecology of malnutrition is complex (Fig. 13.1). It is customary to consider it as:

Table 13.1: Prevalence of undernutrition in India

Indicator	NFHS-2 (1998–1999)	NFHS-3 (2005–2006)
Underweight	43%	40%
Wasting	20 %	23%
Stunting	51%	45%

Abbreviation: NFHS, national family health survey.

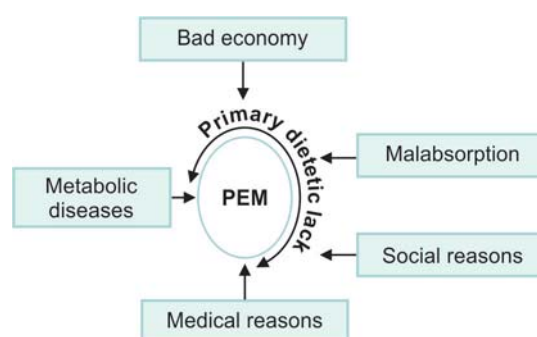


Fig. 13.1: Ecology of malnutrition.

Abbreviation: PEM, protein energy malnutrition.

- **Primary:** It is primarily due to dietary deficiency.
- **Secondary:** It is due to systemic diseases such as tuberculosis or malabsorption.

In a considerable proportion of cases, both the factors may be operative. Even children with the so-called **isolated PEM** without any superimposed infection or infestation do demonstrate some degree of absorptive defect which further aggravates the state of undernutrition.

Bad Economy

(Food Insecurity)

Poor socioeconomic status of the family contributes a lot to the development of malnutrition in the developing regions. With very low income, it is a tough task to provide nutritious diet to the children. It is estimated that, among the downtrodden, hardly 10% of the money is spent on foods obtained from animal sources, i.e. egg, milk, curd and meat etc. With the further pressure on the meager income from increasing requirements, including clothing and entertainment, during modern times, still more curtailment of expenditure on food results.

Ignorance

Food insecurity may not always be the cause of primary undernutrition. Despite availability of food, the child may

- 198** develop undernutrition as a consequence of factors such as ignorance, erratic feeding practices, irrational beliefs and superstitions and poor access to health facility, etc.

Faulty Food Habits and Feeding

Many deep-rooted beliefs, customs, practices, superstitions, food taboos and ignorance join hands to cause malnutrition. Many families frown at the idea that semisolids should be introduced early enough, when the infant is about six months old. They wish to wait until the infant begins to approach the first birthday for a date from the priest to start semisolid food at a ceremony called *annaparasana*. By this time the infant is perhaps already anemic and having some degree of PEM.

Decline in the good practice of breastfeeding just because ignorant mothers wish to ape the sophisticated city women, leading to the widespread practice of artificial feeding, providing diluted and most probably, dirty formula, is today contributing considerably to malnutrition.

Great reliance on milk, which may be awfully diluted, continues to dominate the scene even in educated and well to do families. We have seen mothers complaining that their toddlers are failing to thrive (FTT). On enquiry, it is revealed that these children have been almost entirely on milk and virtually no solids.

Most parents would withhold all foods other than diluted milk once the child has some illness like diarrhea, measles, or abdominal pain—a practice which is bound to deteriorate child's nutritional status.

Yet another limiting factor in adequate nutrition is the belief that certain foods are not given to the baby just because they are said to be *hot* or *cold* in nature.

Medical Reasons

Infections and disorders such as diarrhea, malaria or measles may prove major contributory factors in the development of malnutrition, indirectly or directly. Besides the deliberate restriction of food by the parents, child's intake may be reduced due to reduced appetite. At the same time, there may result more catabolism to produce the heat energy lost during a febrile episode.

Intestinal parasitic infestations may either deprive the host of nutrients or lead to malnutrition by reducing appetite, causing diarrhea, or by producing absorptive defect.

Large Families

Nutritional status is adversely affected by the large size of the family. It has been convincingly demonstrated that malnutrition is much higher among children of birth order fourth and higher than in the first three children of a sibling ship. When there are too many children, the family has to do with whatever food it can manage. The brunt of the suffering falls on the preschool children and the mother.

Closely-spaced Families

There is an evidence that when pregnancies occur rapidly, perhaps every year, or every other year, incidence of malnutrition is much higher. Ideally, there should be at least three years gap between the two pregnancies.

Working Mother

It is a common observation that a higher proportion of the mothers of malnourished children are daily laborers who find little time to take care of child's feeding and rearing. More often than not, mothering is done by an elder sibling.

Bad Start

A LBW infant starts life with a handicap. He is difficult to feed and is vulnerable to infections. Born usually to malnourished mothers, such infants have high mortality. The survivors have poor growth as compared to normal ones.

Secondary Malnutrition

The causes are diseases such as intestinal malabsorption (say celiac disease, tropical sprue, cystic fibrosis, etc.) tuberculosis, intestinal parasitic infestations, diabetes, galactosemia and other metabolic disorders. Mismanagement of diarrhea with starvation therapy or hypocaloric diet (still a common practice in developing countries) is an important cause of malnutrition.

PATHOPHYSIOLOGY

Virtually all organs are affected in malnutrition (Box 13.1).

ASSESSMENT OF NUTRITIONAL STATUS

Though frank cases of kwashiorkor and marasmus cause little difficulty in their identification, assessment of nutritional status may be rather difficult, especially in borderline nutritional disturbances such as mild moderate malnutrition. Furthermore, assessment of nutritional status concerns:

- Individual levels as in hospital/health facility
- Large groups and segments of child population, e.g. times of natural calamities/disasters (earthquake, floods and starvation outbreaks).

The overall criteria employed for assessment of nutritional status are listed in Box 13.2.

Box 13.1

Adverse effect of malnutrition on systems/organs

- **Central nervous system (CNS):** Retarded brain growth (microcephaly), cerebral atrophy; auditory brainstem and visual evoked potential abnormalities; dendritic arborization and dendritic spine abnormalities.
- **Gastrointestinal intestines (GIT):** Smooth tongue because of flattening of papillae; mucosa atrophic and shiny; small intestinal villous atrophy of variable magnitude depending on severity of malnutrition; reduced disaccharides level in brush border; rectal prolapsed.
- **Liver:** Fatty in edematous malnutrition (kwashiorkor and marasmic kwashiorkor); shrunk in marasmus.
- **Pancreas:** Predominant involvement of exocrine pancreas, leading to extraintestinal steatorrhea; reduced insulin level; reduced glucagon production.
- **Endocrines:** Adrenals atrophied; thyroid involution and fibrosis; high growth hormone level
- **Lymphoreticular system:** Lymphocytic depletion; thymus involution.

Box 13.2 Major criteria for assessment of nutritional status in children

- Dietary history
- Clinical signs
- Anthropometry
- Investigations
- Associated disorders
- Vital statistics
- Ecological factors.

Box 13.3 Grading of edema according to severity

- **Grade 1 (Mild):** Both feet and ankles
- **Grade 2 (Moderate):** Both feet and ankles + legs, forearms and hands
- **Grade 3 (Severe):** Generalized including face.

Dietary History

The assessment must begin with the dietary history. Details about intake of cereals, vegetables, pulses, fruits, eggs and meat, etc. and thereby average daily consumption of proteins and calories should be obtained. A rough idea about the adequacy of vitamins and minerals in the diet should also be formed.

Clinical Signs

Deficiency signs such as hair changes, anemia, edema (Box 13.3), xerosis, cheilosis, angular stomatitis, rachitic rosary, bleeding spongy gums and dental caries, etc. should be actively looked for.

The observations on the deficiency signs should, however be interpreted very cautiously. As for instance, phrynodema (toad skin), though traditionally thought to be due to vitamin A deficiency, may also be a feature of scurvy and deficiency of linoleic acid.

Anthropometry

Anthropometry is a very valuable index for evaluation of nutritional status.

Age-dependent Indices

- **Weight for age** is by far the simplest, the most widely used and the most reliable index, provided that it is recorded correctly and is related to the correct age of the individual. See Chapter 3 (Normal Growth). Also, what is more important is the serial record of child's weight periodically on a growth chart.
- **Weight for height** is useful when actual age is in doubt.
- **Height for age** is of no use for detecting early PEM. Its value lies in detecting chronic malnutrition and stunting.

Age-independent Indices

Since, it is often difficult to find true age of the child in the underprivileged and ignorant sections of society, the certain truly or relatively age-independent indices of nutritional status are recommended (Box 13.4).

- **Weight for height**, which is only partially age-independent, is calculated as follows:

Box 13.4 Age-independent indices for assessment of nutritional status

- Weight for height
- Mid-upper arm circumference
- Mid-upper arm muscle circumference
- Triceps skinfold thickness
- Chest/head circumference ratio
- Quaker upper arm circumference (QUAC) stick method
- Mid-upper arm/height ratio
- Shakir's tape
- Bangle method
- Dugdale index
- Rao's weight/height ratio
- Kanawati index
- Body mass index
- Ponderal index
- Quetlet index.

$$\text{Percentage weight for height} = \frac{\text{Actual weight} \times 100}{\text{Expected weight for actual height}}$$

- **Nabarrow's thinners chart**, based on weight for height, is recommended by **save the children fund**. The child is made to stand against the chart which bears the expected weight for height. The child's head touches the upper red zone in the presence of severe PEM.
- **Mid-upper arm circumference (MUAC)** is measured midway between the point of the shoulder (tip of acromion process) and olecranon process of ulna. For all practical purposes, the maximum circumference of the upper arm measured when the left arm is hanging by the side of the body would do. Between 1 and 5 years, it remains constant between 16.25 and 16.75 cm. This is because of replacements of the baby fat with muscle tissue. Any child in this age group with a circumference less than 11.5 cm of the reference international standard is to be considered suffering from severe malnutrition, between 11.5 cm and 12.5 cm from moderate malnutrition, and between 12.5 and 13.5 cm from mild malnutrition. For exact figures regarding mid-arm circumference at various ages see Table 3.2.
- **Mid-upper arm muscle circumference (MUAMC)** is calculated by the following formula:

$$\text{MUAMC} = \text{MAC} - \pi \times \text{triceps skin fold thickness.}$$
- **Triceps skin fold thickness** is measured by a standard caliper (Lange, Herpenden or Best). Tanner chart gives the normal values at different ages. On an average it exceeds 10 mm in 1–6 years age group. A measurement between 6 and 10 mm points to mild and moderate malnutrition and under 6 mm to severe malnutrition.
- **Chest/head circumference ratio less than one** after first year of life indicates malnutrition.
- **Mid-upper arm/height ratio** of less than 0.29 indicates gross malnutrition, the normal being 0.32–0.33.
- **Quaker upper arm circumference (QUAC) stick method** (Box 13.5) is a simple, easy, inexpensive and yet reliable method of detecting early malnutrition of acute onset in a large number of children in a brief span

Box 13.5 Quaker upper arm circumference (QUAC) stick method

- **QUAC stick** is an abbreviation for Quaker upper arm circumference measuring stick. The instrument consists of a stick graduated with figures for mid-upper arm circumference in relation to height. For this test, maximum left-upper arm circumference (the arm hanging by the side of the body) is recorded. Then, the child is made to stand in front of the QUAC stick. From the graduations in the stick, his nutritional status in terms of 50, 60, 70 or 80% of the standard can be easily read (Fig. 13.2).
- **Modified QUAC stick** utilizes a rod or stick that is colored green (normal nutrition), yellow (borderline nutrition) and red (severe malnutrition).

of time in the community settings, especially during natural calamities such as floods and earthquakes. The instrument is a stick graduated with figures for MUAC in relation to height (Box 13.5, Fig. 13.2).

- **Shakir tape method** is a simple and age-independent tool for assessing malnutrition. This special tape has colored zones—red, yellow and green, corresponding to less than 12.5 cm (wasted), 12.5–13.5 cm (borderline) and over 13.5 cm (normal) MUAC. Now, new tapes showing less than 11.5 cm as severe malnutrition are replacing the old ones in keeping with the WHO recommendations. Also, See Chapter 3 (Normal Growth).
- **Bangle method**, another method not needing age and useful in preschool children, consists of slipping a bangle with a diameter of 4 cm up the forearm. An attempt is made to move it over to the upper arm. In case it can slip over the elbow, malnutrition is present. The method, though simple and easy, is not quite reliable.
- **Dugdale index** too is based on relationship between weight and height. It is expressed as:

$$\text{Dugdale index} = \frac{\text{Weight (kg)} \times 1.6}{\text{Height (cm)}}$$

Normal value varies between 0.88 and 0.97. An index of less than 0.79 suggests malnutrition.

- **Rao's weight/height ratio** is expressed as:

$$\text{Rao's ratio} = \frac{\text{Weight (g)}}{\text{Height (cm)}^2} \times 100$$

Normal value is above 0.0015. A value of 0.0013–0.0015 indicates moderate malnutrition and less than 0.0013 indicates severe malnutrition.

- **Kanawati index**, based on MUAC and head circumference ratio, varies between 0.32–0.33. A ratio of less than 0.25 points to severe malnutrition.
- **Body mass index (BMI):**

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height (m)}^2} = \text{kg/m}^2$$

- **Normal:** 18.5–22
- **Overweight:** 22–25
- **Obesity:** 25–30
- **Mobid obesity:** More than 30
- **Borderline malnutrition:** 15–18.5
- **Moderate malnutrition:** 13–15
- **Severe malnutrition:** Less than 13.

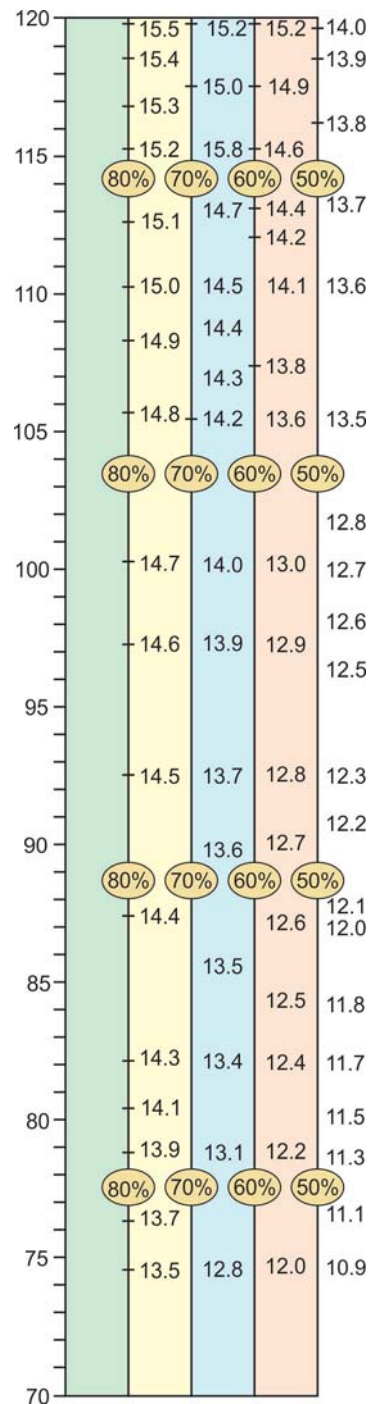


Fig. 13.2: Quaker upper arm circumference (QUAC) stick method.

- **Ponderal index** is expressed as:

$$\text{Ponderal index} = \frac{\text{Weight (g)}}{\text{Length/height (cm)}^3}$$

An index less than 2 points to asymmetrical intrauterine growth retardation (IUGR), more than 2 symmetrical IUGR, 2–2.5 borderline malnutrition, and less than 2 severe malnutrition, and more than 2.5 appropriate for gestational age (AGA).

- **Quetlet's index** is expressed as:

$$\text{Quetlet's index} = \frac{\text{Weight (kg)}}{\text{Length/height (cm)}^3}$$

Normal value varies between 0.14 and 0.16. In gross malnutrition, it is less than 0.14. It is quite reliable. It is similar to BMI, except that here we take height in centimeters rather than meters.

Investigations

- **Laboratory investigations** include complete blood picture especially, hemoglobin, erythrocyte sedimentation rate (ESR), serum proteins and blood levels of nutrients like vitamins, iron, etc.
- **Tuberculin (Mantoux) test** to exclude tuberculosis.
- **Chest X-ray (CXR)** for superadded lower respiratory infection (say pneumonia) and tuberculosis, etc.
- **Special biochemical tests** may detect subclinical malnutrition that could not be revealed by anthropometry.
- **Amino acid level** in blood and urine (Box 13.6) may be helpful in borderline cases. Hydroxyproline is the most commonly used among the amino acids. Hydroxyproline levels are an indicator of collagen content. Conditions that increase collagen turnover can elevate serum and urine hydroxyproline levels. Urine and serum hydroxyproline levels can be used as a marker for bone resorption.

Box 13.6 Serum amino acid patterns in malnutrition

- Amino acid pattern is measured by comparing concentrations of two groups of amino acids using per chromatography as shown:

$$\text{Ratio} = \frac{\text{Glycine} + \text{serine} + \text{glutamine} + \text{taurine}}{\text{Valine} + \text{leucine} + \text{isoleucine} + \text{methionine}}$$

- Mean ratio in normal children is 1.5. In subclinical malnutrition, it is between 2.0 and 4.0. In kwashiorkor, it is above 3.5.
- **Urinary urea/creatinine (U/C) ratio:** This ratio can be expressed by any of two formulas:

$$\text{U/C} = \frac{\text{mg-urea-nitrogen mL}}{\text{mg-creatinine-nitrogen mL}^{-1}}$$

$$\text{U/C} = \frac{\text{mg-urea-nitrogen mL}^{-1}}{\text{mg-creatinine mL}}$$

The reduced ratio is a measure of average protein intake rather than the exact nutritional status.

- **Urinary hydroxyproline index:** The formula for calculating hydroxyproline index (HOP) is as follows:

$$\text{HOP index} = \frac{\text{mmol hydroxyproline mL}^{-1}}{\text{mmol creatinine mL} - \text{body weight}}$$

Normal value varies between 2.0 and 5.0, an index of less than 2.0 reflect growth retardation.

- **Urinary hydroxyproline creatinine ratio:** It is supposed to be better than the HOP index. Its main flaw is that it varies considerably with age. Standard values for different ages are available.
- **Urinary creatinine-height index (CHI):** It is the ratio between the creatinine excreted by the subject in 24 hours and the daily creatinine output of the average normal child of the same height:

$$\text{CHI} = \frac{24 \text{ hour urine creatinine}}{24 \text{ hour urine creatinine for a normal child of the same height}}$$

In kwashiorkor and marasmic kwashiorkor, value varies between 0.25 and 0.75. In nutritional marasmus, it ranges between 0.33 and 0.85. Normal children and those having fully recovered from malnutrition show an index of around unity.

- **3-Methyl histidine excretion:** 24 hour urinary excretion of 3-methyl histidine/kg body weight in malnourished children is reduced to around 33% of that of normal children. With beginning of nutritional rehabilitation, values speedily return to normal.

- **Hydroxyproline assay kit** is suitable for hydroxyproline detection in cell and tissue culture supernatants, urine, plasma, serum, and other biological samples. Salivary protein, salivary ferritin and free α -amino nitrogen in leukocyte are reduced in malnutrition.
- **Skeletal radiographs** may reveal some retardation of bone age, osteoporosis or classical signs of nutritional rickets or scurvy. Some workers have described transverse lines of arrested growth at the growing ends of long bones months prior to onset of frank PEM.

Assessment for Associated Disorders

While assessing the nutritional status, one must ascertain for evidence of intestinal parasitic infestations, malabsorption and tuberculosis, etc.

Vital Health Statistics

For evaluation of the nutritional status of a community, the above measures should be supported by vital statistics such as under five mortality, infant mortality, neonatal mortality, perinatal mortality, stillbirth rate and life expectancy as also the ecological background.

Ecologic Factors

Malnutrition is the result of a multitude of ecologic factors. Understandably, it is important to obtain ecologic information on factors such as:

- Food consumption by the community.
- Socioeconomic factors such as knowledge, attitudes, practices (KAPs), beliefs about feeding, education and income.
- Health and education services, e.g. feeding programs, immunization facilities.
- Conditioning influences, e.g. infections that are known causes of precipitating malnutrition.

PROTEIN ENERGY MALNUTRITION (PEM): A SPECTRUM

The term, PEM, refers to a class of clinical conditions that may result from varying degree of protein lack and energy (calorie) inadequacy. The term has been adopted because it is now widely agreed that the major limiting factors in the diet of children, particularly in the resource-limited countries, are energy and proteins, usually more of the former. Deficiency of proteins is usually not primary and isolated. Almost always it appears to be due to poor intake of food (energy) as such. There is evidence that if child's energy is taken care of, it will be difficult for him to have significant protein deficiency. Else, if his energy consumption is poor, whatever proteins he takes are likely to be consumed to provide energy rather than to build the tissues.

Among the various factors that influence the clinical manifestations of PEM figures:

- Magnitude of deprivation, its duration, relative inadequacy of different principles of food,
- Accompanying infection or some other disease.

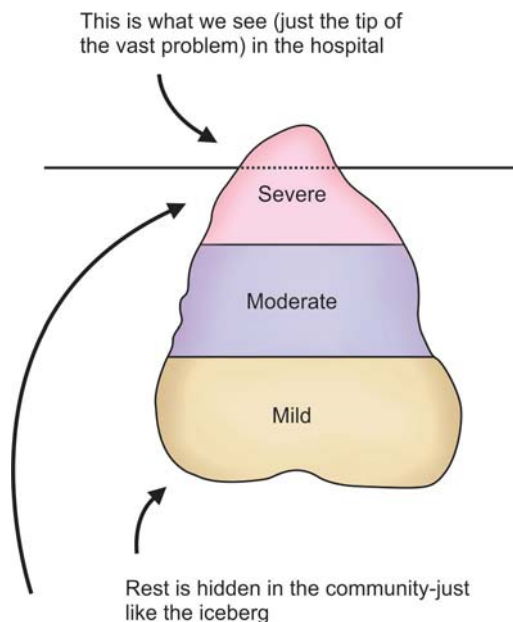


Fig. 13.3: Malnutrition (tip of iceberg).

Broadly speaking, two major clinical syndromes, kwashiorkor and nutritional marasmus, are widely recognized.

1. **Kwashiorkor** is said to result from gross deficiency of proteins though energy deficiency is also present.
2. **Nutritional marasmus**, on the other hand, results from gross deficiency of energy though protein deficiency also accompanies.

Thus, it is clear that there is deficiency of both, proteins and energy, in both the states. The predominance of the deficiency determines whether it is going to be kwashiorkor or nutritional marasmus.

Many malnourished children show overlap in the clinical picture, demonstrating features of both the deficiency states at a time. It is often quite appropriate to label them as marasmic kwashiorkor. But, the aforesaid severe form of PEM constitutes only a tip of the widespread problem of malnutrition (Fig. 13.3). A vast majority of the children suffering from mild to moderate forms of it remain hidden in the community for one or another reason. The two types of this subclinical malnutrition are—(1) nutritional dwarfing (stunting) and (2) prekwashiorkor.

All these form of PEM, in actuality, constitute a continuous spectrum of the manifestations of malnutrition. Growth failure and poor tissue repair (due to protein lack) and energy shortage (due to calorie deficiency) are common to all forms.

EVOLUTION OF PEM

Dietary Hypothesis

According to the widely accepted dietetic hypothesis, kwashiorkor is predominantly a protein deficiency and marasmus an energy deficiency. Of course, both proteins and energy lack-exist in both the syndromes. This hypothesis has a good deal of support from studies in the laboratory animals as well as work on human beings.

Adaptation Hypothesis

The noted nutritionist, Gopalan, has claimed that dietary background of children suffering from kwashiorkor and marasmus may well be the same. According to his postulation, the so called **adaptation hypothesis**, marasmus is an extreme degree of adaptation to prolonged inadequacy of proteins and energy in the diet. Kwashiorkor is a stage of adaptation failure or dysadaptation which may follow two situations:

1. Continued prolongation of the stress of malnutrition
2. Sudden precipitation or aggravation by a fulminant infection such as measles, pertussis, bronchopneumonia or acute diarrheal episode.

Gopalan feels that whereas nutritional marasmus may be the result of extreme degree of adaptation and the kwashiorkor the result of dysadaptation, relatively mild effect of adaptation may be responsible for nutritional dwarfing. Since, according to Gopalan's hypothesis, kwashiorkor follows occurrence of dysadaptation in a marasmic child, most of the cases are likely to show features of both, i.e. marasmic kwashiorkor.

Aflatoxin Contamination Hypothesis

More recently, it has been postulated that aflatoxin contamination of food may well be an important factor in the causation of kwashiorkor.

Golden's Hypothesis of Free Radicals

According to Golden's hypothesis of free radical damage, kwashiorkor results from overproduction of free radicals (because of infection, toxins, iron, etc) and breakdown of protective mechanism (provided by vitamin A and E, carotene, zinc, copper, selenium and manganese, etc).

Jelliffe's Hypothesis of Interactions and Sequelae

According to Jelliffe, kwashiorkor is an intrinsically nutritional disorder with vulnerability to other factors, some identified and some unidentified. It is the cumulative result of a mixture of interactions and sequelae of dietary imbalances and/or deficiency, infections, parasitosis, emotional trauma from maternal deprivation due to abrupt weaning from breasts, toxins like aflatoxin or ochratoxin.

PEM AND DISTURBANCES OF METABOLISM

Many like to designate PEM as a **metabolic disorder**. This is quite understandable if we recall that the disease is characterized by profound disturbances of water and electrolytes, minerals, protein, fat, carbohydrate and energy metabolism.

Water, Electrolytes and Minerals

- **Total body water:** Total body water is increased in PEM, irrespective of whether it is of kwashiorkor or marasmic type. A positive correlation exists between the magnitude of rise in body water and the extent of weight loss. Thus, lowest values are found in kwashiorkor and the highest in marasmus.

Whether the alteration is secondary to increased cellular mass which constitutes the active protoplasm of the body and reduction in the adipose tissue is not clearly understood. A noteworthy point is that despite increased body water, a malnourished child is thirsty. This paradoxical observation is ascribed to the defective thirst mechanism in PEM.

- **Potassium:** There is a definite reduction in the total body potassium by as much as 25%. Though all organs are depleted of potassium, the musculature suffers the most followed by the brain. Potassium depletion is more marked in cases of PEM with diarrheal disease. In kwashiorkor, it is significant even in the absence of diarrhea. Whether potassium depletion results from gastrointestinal losses through the gut or from defects in specific enzymes (that have a role in carbohydrate metabolism), or both, is not clear. Potassium deficiency may be existing despite absence of any clinical manifestations of dehydration and/or hypokalemia. A very high frequency of pyelonephritis and acute renal failure is encountered in cases of severe malnutrition whose potassium depletion has not been attended to. Of course, the contributory role of concomitant dehydration and infection cannot be denied.
- **Sodium:** Unlike potassium depletion, sodium is retained by the body. Sodium retention is primarily extracellular though muscle, skin, brain and viscera, too, are affected. Intracellular sodium retention and potassium deficit may change the function of important enzymes in carbohydrate metabolism and oxidative phosphorylation.
- **Magnesium:** Its depletion in PEM is now well established. This deficiency may cause grave disturbances, including neurologic signs such as twitching, tremors and convulsions.
- **Phosphorus:** Both forms of phosphorus (organic as well as inorganic) are decreased in the muscles of malnourished children. Adequate nutritional correction leads to increase in both the forms. The exact significance of this observation, particularly from a clinical angle, remains obscure.
- **Calcium:** Its depletion is a common feature of PEM, more so when the assessment is based on blood levels. However, clinical evidence of tetany is infrequent.
- **Iron:** Iron deficiency anemia is a common feature of PEM. It is, however, complicated by other deficiencies involving folic acid, vitamin B₁₂ vitamin E and probably some other vitamins.
- **Copper:** Low levels of copper in serum, hair and liver of subjects suffering from PEM have been documented. There may also be low levels of ceruloplasmin which plays the role of a link in copper and iron metabolism.
- **Chromium:** Its deficiency has been blamed for the impaired glucose tolerance in malnourished children. There is evidence that it may contribute to poor growth of the child during the earlier stage of nutritional rehabilitation. Chromium therapy may accelerate growth in marasmic infants.

- **Zinc:** Low serum as well as muscle and liver zinc values exist in PEM. Zinc deficiency may play an important role in the etiology of the syndrome of growth retardation with short stature, hypogonadism, hepatosplenomegaly and anemia in boys. The supplementation of zinc to such boys results in a dramatic improvement. Sometime, within three weeks of initiating treatment, significant gain in weight and acceleration of sexual maturity are achieved. Zinc deficiency is also associated with infantile tremor syndrome and diarrheal disease.

Protein and Amino Acids

Total serum protein level is always reduced, principally due to hypoalbuminemia which is remarkable in kwashiorkor. The level of β -globulins is also reduced. α and γ -globulin level is variable in absolute terms; it is invariably high in relation to other serum protein fractions.

There is a remarkable reduction in the total body protein. Its turnover, unlike that of albumin, may be high rather than low. Significant reduction in plasma amino acids occur in kwashiorkor. Valine, leucine, isoleucine and tyrosine are the ones most affected. There is a rise in amino acid recycling in kwashiorkor. This mechanism, together with low urea synthesis, increased ammonia and urea nitrogen utilization for protein synthesis, contributes to increased nitrogen economy in protein deficiency.

Lipids

There is a reduction in fat absorption from the gut. Also, there is increase in fecal fat (steatorrhea) even when diet is free from fat. Free bile acids are increased whereas there is a decrease in the concentration of conjugated bile acids. The latter are supposed to be essential for dissolution of lipids in the lumen of the gut and their eventual absorption.

The transport of fat from liver to tissues as low density lipoproteins is considerably reduced though transport from gut to liver is not much altered. Various factors that may contribute to the fatty liver of kwashiorkor are increased fat transport from tissues to liver, reduced synthesis of β -lipoproteins, increased liver lipogenesis, and probably reduced level of essential fatty acids.

Carbohydrates and Energy

Hypoglycemia occurs frequently and may prove fatal in a proportion of cases. Glucose absorption is impaired due to deficiency of disaccharides enzymes in the intestinal mucosa. Handling of intravenously administered glucose and galactose is abnormal. Circulating insulin levels are low. The levels fail to respond to stimulation with glucose or arginine.

Disaccharide intolerance is a common transient phenomenon. Hence, it is advisable to avoid large loads of lactose containing foodstuffs during early part of management of PEM. Levels of growth hormone are high, but of somatostatin low. Basal metabolic rate (BMR) is reduced. Thyroid function, too, is low.

There is a considerable evidence supporting the definite association between malnutrition and infection. Malnutrition is the most common immunodeficiency in pediatric practice and breaks down the host resistance in by and large all segments (Figs 13.4 and 13.5). The most consistent abnormality is impairment in cell-mediated immunity (CMI). The implications of this observation are:

- Bacterial infections, which count on CMI for host's defense against them, are very severe in children suffering from PEM.
- Secondly, children with PEM are difficult to sensitize by repeated antigens.
- Even the delayed hypersensitivity reactions that recall previous sensitization are also delayed.

There is evidence that iron deficiency anemia has an adverse effect on the cellular immune response. The underlying mechanisms include:

- Lymphopenia
- Reduced number of T-lymphocytes in the peripheral blood
- Impaired response to mitogen and antigens
- Decreased lymphokine production
- Serum inhibition.

It has been demonstrated that levamisole improves the ability of lymphocytes to proliferate *in vitro* in response to phytomitogens and increases the number of rosetting T-lymphocytes. However, the effect on lymphocyte stimulation response is less than that achieved by nutritional supplementation both at 2 and 4 week intervals after initiation of therapy. When given together with nutritional rehabilitation, levamisole administration

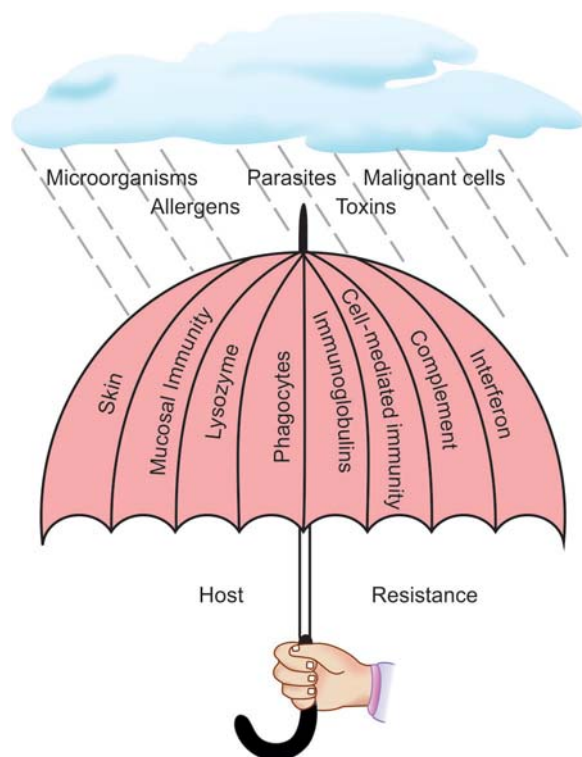


Fig. 13.4: Host resistance in a healthy, well-nourished child provides protection against adverse influences and insults.



Fig. 13.5: Immunodeficiency secondary to malnutrition. Note the widespread breakdown in host resistance, involving almost all organ and systems.

Box 13.7 Interrelationship between PEM and infection

Causes of malnutrition leading to infection

- Micronutrient deficiency—iron, zinc, copper and selenium
- Vitamin deficiency—vitamin A, C, E, B₆ and folate
- Impaired CMI, phagocytic function and complement system
- Reduced cytokine production
- Reduced concentration of IgA, IgM and IgG.

Cause of infection leading to malnutrition

- Reduced intake of food, especially micronutrients
- Enhanced catabolic losses
- Reduced absorption of nutrients
- Metabolic inefficiency because of micronutrient deficiency.

Abbreviations: CMI, cell-mediated immunity; PEM, protein energy malnutrition; Ig, immunoglobulin.

is associated with an increase in cell-mediated response *in vivo* and *in vitro*. The change is observed earlier than a significant gain in weight.

Interrelationship between PEM and infection is summarized in Box 13.7.

PEM AND DIARRHEA

Diarrhea is a common accompaniment of the clinical picture of overt PEM. Its prevalence is 5–7 times more and its severity 3–4 times greater in malnourished children as compared to normal children. In the not-so-distant past, recurrent diarrhea in malnourished children was generally ascribed to superimposed infections and infestations. No doubt, malnourished patients are particularly susceptible to infection because of the impaired cellular immunity which is an important adverse sequel of malnutrition per se.

Box 13.8 Factors contributing to diarrhea in PEM

- Superimposed gastrointestinal infection—bacterial, parasitic, fungal
- Villous atrophy causing malabsorption
- Disaccharidase deficiency in brush border, causing transient lactose intolerance and osmotic diarrhea
- Iron deficiency anemia causing exudative enteropathy
- Pancreatic insult causing digestive disturbances, steatorrhea and diarrhea.

- It was earlier suggested that, besides bacterial and parasitic contamination of the gut, gastrointestinal candidiasis may contribute to the common occurrence of diarrhea in malnutrition. The investigations from Indonesia and Australia lend support to this hypothesis.
- PEM may per se cause striking morphological as well as functional damage to the small intestinal mucosa, leading to malabsorption.
- Transitory secondary disaccharides deficiency, causing lactose intolerance and osmotic diarrhea has also been observed in significant proportion of cases. The earlier reports suggesting existence of some monosaccharide malabsorption have now been substantiated.
- Moreover, it is to be noted that iron deficiency is a common occurrence in PEM. Since there is evidence that iron deficiency may itself contribute to an exudative enteropathy in childhood, the role of such anemia in etiology of diarrhea of malnutrition seems to be convincingly established.
- A recent study has documented significant decline in histamine augmented maximum acid output as also presence of chronic gastritis and gastric mucosal atrophy in per oral gastric biopsies in marasmic children.
- Finally, there is evidence that PEM may give rise to pancreatic atrophy and decreased enzyme secretion, resulting in digestive disturbance and diarrhea. Thus, it becomes obvious that diarrhea in malnutrition is of multifactorial etiology (Box 13.8).

PEM AND FAMILY PLANNING

In developing countries, women (often malnourished) begin to produce children at a much younger age. They continue doing so quite frequently with poor spacing. Result is in the form of too many births. What is still more disturbing is that they continue doing so as long as they are not old enough.

This phenomenon leads to impaired nutritional status of both the mother and her babies, many of whom may be born after intrauterine growth retardation has already affected their bodies and perhaps brains. Such infants start life with a distinct disadvantage. They are also candidates for high morbidity and mortality. Undoubtedly many of such deaths could be prevented. The biostatisticians call such deaths as excessive **reproductive wastage**.

The question arises, **Why do women reproduce at such a high pace in developing world?** The reason is simple. Unless parents can be assured that the children they have are going to survive into adulthood, they will be unwilling to consider limiting their reproductive activities.

It has, therefore, been argued that nutrition and general health activities should be coordinated to provide major support for maintaining health and promoting survival of infants and children.

A strong plea is made for promoting the traditional breastfeeding with suckling done throughout the 24 hours each day. This practice is not only a safeguard against malnutrition, but it also has an effect on ovulation and birth spacing.

PEM AND ENDOCRINE STATUS**Cortisol**

Contrary to earlier studies, now it has been convincingly shown that serum cortisol levels in gross PEM are high, suggesting hyperfunction of the adrenal cortex. Factors such as infection and hypoglycemia are said to contribute to this observation. High cortisol levels mediate the following useful functions:

- Augmentation of lipolysis
- Enhancement of muscle protein catabolism
- Promotion of liver protein synthesis.

Somatomedins

Serum levels of insulin like growth factor (IGF-1 and 2) are low due to one or more of the following factors:

- Low protein and/or energy supply in diet
- Lack of essential amino acids
- Low insulin/cortisol ratio.

Low somatomedins levels mediate the useful function of reducing energy and oxygen utilization by retarding growth.

Insulin

Impaired serum insulin levels are found in kwashiorkor and marasmic kwashiorkor, but not in marasmus due to:

- High energy low protein ratio in diet
- Low body potassium
- Deficient insulinotropic factors and insulin transport by the damaged pancreas.

Growth Hormone

Growth hormone levels are high in PEM, reflecting increased secretion rather than impaired clearance. The causative factors include:

- Low somatomedin levels
- Hypoalbuminemia and low amino acid levels
- Low serum tyrosine level.

The useful functions mediated by the above observations include:

- Facilitation of the process of lipolysis
- Boosting of glucogenesis
- Decrease in catabolism of albumin.

Glucagon

Glucagon levels are high whereas insulin levels are low in PEM, leading to low insulin/glucagon ratio. The following useful functions may be mediated:

- 206 ■** Reduction in glucose uptake by muscles and adipose tissue, sparing heart and brain
- Increased muscle protein catabolism
 - Increased lipolysis and fatty acid supply to peripheral tissues.

Thyroxin

Contrary to earlier observations, thyroid hormone production is either normal or high in kwashiorkor, but normal or low in marasmus.

PEM AND CARDIAC FUNCTION

Gross malnutrition is known to considerably reduce the weight and the size of the heart. This is ascribed to atrophy of the cardiac muscle. On the functional front, cardiac output is reduced in keeping with the severity of weight loss. There is prolongation of the systemic recirculation time, appearance time, bradycardia and reduced peripheral blood flow. Congestive cardiac failure (CCF) may occur. Electrocardiography (ECG) shows nonspecific changes. Radiology shows reduction in heart size. Not only does malnutrition per se affect cardiac function, but other factors such as accompanying severe anemia, reduced oxygen consumption and hypothyroid state too contribute to it.

PEM AND RENAL FUNCTION

PEM causes reversible impairment of renal function as manifested by:

- Reduction in glomerular filtration and renal plasma flow, especially when there is accompany gastroenteritis.
- Aminoaciduria, phosphaturia and inefficient excretion of acid load from disturbed tubular function.
- Urine is acidic due to increased excretion of hydrogen ions to conserve potassium.

PEM AND DRUG DISPOSITION

It is now well established that nutritional status of a child has significant effect on the bioprocesses involved in disposition of various drugs in the body. As a result, bioavailability of the drug(s) for therapeutic purposes is influenced, often warranting alteration in dose and frequency of administration. The exact observations concerning different drugs in various studies, however, are far from uniform.

VARIOUS CLASSIFICATIONS OF PEM

Based on Clinical Features

Syndromal Classification

- Kwashiorkor
- Marasmus
- Marasmic kwashiorkor
- Prekwashiorkor
- Stunting
- Underweight
- Invisible PEM.

Based on Weight for Age

Gomez Classification

- **First degree:** Weight between 90 and 75% of expected for age
- **Second degree:** Weight between 75 and 60% of expected for age
- **Third degree:** Weight below 60% of expected.

Wellcome or International Classification

- **Weight between 80 and 60% of expected for age with edema:** Kwashiorkor
- **Weight between 80 and 60% of expected for age without edema:** Undernutrition
- **Weight below 60% of expected with edema:** Marasmic-kwashiorkor
- **Weight below 60% of expected without edema:** Marasmus.

Indian Academy of Pediatrics (IAP) Classification

- **First degree:** Weight between 80 and 70% of expected for age
- **Second degree:** Weight between 70 and 60% of expected for age
- **Third degree:** Weight between 60 and 50% of expected for age
- **Fourth degree:** Weight below 50% of expected in case the child has demonstrable pitting edema, the letter "K" is placed in front of the evaluated grade.

Jelliffe Classification

- **First degree:** Weight between 90 and 80% of expected for age
- **Second degree:** Weight between 80 and 70% of expected for age
- **Third degree:** Weight between 70 and 60% of expected for age
- **Fourth degree:** Weight below 60% of expected.

All these classifications recommended Harvard standard as the reference standard (now obsolete). WHO 2006–2007 reference standards are the current recommendation.

Based on Weight for Height

Waterlow Classification

- **Weight more than 90% of expected for height:** Normal
- **Weight 80–90% of expected for height:** I degree
- **Weight 70–80% of expected for height:** II degree
- **Weight less than 70% of expected for height:** III degree.

MacLaren Classification

- **Weight more than 90% of expected for height:** Normal
- **Weight 85–90%:** Mild (I degree)
- **Weight 5–85%:** Moderate (II degree)
- **Weight less than 75%:** Severe (III degree).

Based on Height for Age

Waterlow Classification

- **Normal:** 98%
- **Mild:** 95–90%
- **Moderate:** 85–90%
- **Severe:** Less than 85%.

Based on Weight for Height and Height for Age

Waterlow Classification

- **Acute:** Weight for height low, height for age (normal, wasted not stunted)
- **Acute/chronic:** Weight for height low, height for age low (wasted and stunted)
- **Nutritional dwarfing:** Weight for height normal, height for age low (stunted but not wasted).

Application of both the indices (as in Waterlow classification) is, therefore of greater value than application of one.

WHO Classification

The WHO classification of PEM is given in Table 13.2 and shown in Figure 13.6.

Based on MUAC

Arnold Classification

- **Mild:** MUAC between 12.5 and 13.5 cm
- **Moderate:** MUAC between 11.5 and 12.5 cm
- **Severe:** MUAC under 11.5 cm.

Based on Skinfold Thickness

- **Mild:** 80–90% of expected for age (8–9 mm)
- **Moderate:** 60–80% of expected for age (6–8 mm)
- **Severe:** Less than 60% of expected for age (less than 6 mm).

Table 13.2: WHO classification of PEM		
Criteria	Moderate PEM	Severe PEM
Symmetrical edema	No	Yes
Weight for height (Index of wasting)	70–79% of expected (Wasting)	Less than 70% of expected (Severe wasting)
Height for age (Index of stunting)	85–89% of expected (Stunting)	Less than 85% of expected (Severe stunting)

Abbreviations: PEM, protein energy malnutrition; WHO, World Health Organization.

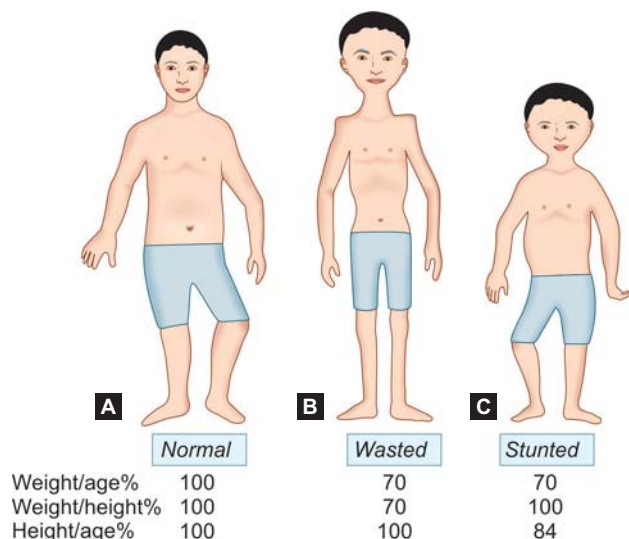


Fig. 13.6: Normal wasted and stunted children. Weight for age is low in both wasted child and the stunted child. But weight for height is not affected in the stunted child.

Based on BMI (kg/m²)

- **Mild (underweight):** 15–18.5
- **Moderate:** 13–15
- **Severe:** Less than 13
- **Normal:** 18.5–22
- **Overweight:** 22–25
- Unlike adults, in children 25–30 is considered obesity
- **More than 30:** Moribund obesity.

- Weight for height = $\frac{\text{Actual weight}}{\text{Weight of normal child of the same age}} \times 100$
- Height for age = $\frac{\text{Actual height}}{\text{Height of normal child of the same age}} \times 100$
- Currently, reference norms for comparison are WHO (2006–2007) standards.

SPECIAL FEATURES OF CLINICAL SYNDROMES

Kwashiorkor

(Edematous Malnutrition, Malignant Malnutrition)

The earliest description of kwashiorkor in the English medical literature was made in 1933 by Cicely Williams, a noted British physician. That time she did not really know how to christen the disease. Later, in 1935, she introduced the term **kwashiorkor**, the local name for the disease in Ghana. It was said to mean the **red boy**, because of the characteristic pigmentary changes. In 1950, the term was more aptly interpreted to apply to the mystique of the disease that affected the deprived child due to the arrival of yet another.

Clinical Features (Figs 13.7 to 13.9)

The disease is chiefly encountered in infants and children in the preschool age group. A vast majority of the cases are in 1–4 years age group. No age is, however, exempt. Occasionally, it may be seen in infants aged few months, in adolescents and even in adults. A classical case of kwashiorkor is:



Fig. 13.7: Kwashiorkor. Note the classical features, including growth retardation, remarkable muscle wasting with some retention of subcutaneous adiposity and nutritional edema and psychomotor changes. Protuberant abdomen seen in these two children is frequently present.



Fig. 13.8: Kwashiorkor. Note massive edema and flaky-paint dermatosis.



Fig. 13.9: Kwashiorkor. Note the flaky-paint dermatosis and essential features (growth retardation, edema, muscle wasting with retention of some subcutaneous adiposity and psychomotor change) in this 24-month-old boy weighing only 8 kg (including weight of edema fluid).

Table 13.3: Grading of kwashiorkor

Grades	Characteristics
1	Pedal edema
2	+ Puffiness of face
3	+ Edema of chest wall and back
4	+ Ascites

Note: Grading of kwashiorkor based on edema is not the same as grading of edema as such.

- Dull, apathetic and miserable, evincing hardly any interest in the surroundings
- His growth is stunted
- Marked muscle wasting with some retention of subcutaneous fat
- He has pitting edema over the legs and feet and perhaps over certain other parts of the body (Table 13.3).

There may be diarrhea, skin and hair changes, and anemia and vitamin deficiency signs. Liver is, as a rule, enlarged due to fatty change.

Though this is the picture of full-blown kwashiorkor, it may be noted that only four signs (growth failure, muscle wasting with retention of some subcutaneous fat, mental apathy and hypoalbuminemic edema not of cardiac, renal or hepatic origin) taken together are sufficient by themselves to label a case as kwashiorkor. The remaining elements may individually or collectively accompany the essential features, depending on the severity of the disease, dietary pattern and regional variations.

Biochemical Changes

These are striking:

- Serum proteins are always low, the maximum reduction being that of the albumin fraction; the globulins may often be found relatively elevated.
- Anemia is usually moderate to severe and may be of variable morphology though iron-deficiency is a common denominator in most cases.
- Low serum enzymes (esterase, amylase, lipase, cholinesterase and alkaline phosphatase), serum cholesterol, glucose, urea, certain vitamins, potassium and magnesium occur. The activity of pancreatic enzymes is considerably reduced.
- Total body potassium is diminished.
- Imbalance of plasma amino acids and amines aciduria are common findings.
- Impaired cellular immunity is present.

Diagnosis

Dietetic enquiry reveals deficient intake of proteins and calories, the protein lack being more predominant over a prolonged period. Occurrence of an added stress like measles, whooping cough, diarrhea or bronchopneumonia often precipitates the overt picture, leading to development of pitting edema. Diagnostic criteria may be divided into two major subdivisions—(1) essential and (2) nonessential.

Essential Features

(Minimal Diagnostic Criteria)

- Growth retardation as evidenced by low weight and low height.
- Muscle wasting with retention of some subcutaneous fat.
- Psychomotor change as evidenced by mental apathy in the form of silent listless inertness, lack of interest in the surroundings.
- Hypoalbuminemic pitting edema, at least over the pretibial region. Serum albumin should be less than 2.5 g/dL and cardiac, hepatic, renal and angioneurotic causes of edema should be ruled out. These essential features are to be considered the minimal diagnostic criteria for kwashiorkor.

Nonessential Features

These are variable features and may or may not be present in each and every case.

- **Hair changes (Figs 13.10 and 13.11)** in the form of hypochromotrichia (light-colored hair), sparseness (areas of alopecia), change in texture (coarseness,



Fig. 13.10: Kwashiorkor. Note the characteristic mental apathy, moon facies with periorbital edema and sparse light-colored hair.



Fig. 13.11: Kwashiorkor. Note the psychomotor changes, light-colored sparse scalp hair, moon facies, periorbital edema, and pedal edema.



Fig. 13.12: Kwashiorkor showing massive edema over feet and legs as also mosaic dermatosis. This is the same child as in Figure 13.10.



Fig. 13.13: Kwashiorkor. Note the classical flaky-pain dermatosis and massive edema. Absence of hair changes reflects acute nature of the ailment.

silkeness) and easy pluckability. Alternate bands of light and dark color have earned the name flag sign which signifies periods of inadequate, adequate and inadequate nutrition over a prolonged period. This fascinating sign is only occasionally encountered.

- **Skin changes** include light-colored skin, but the most classical dermatosis consists of areas of hyperpigmentation intervened by areas of raw red skin caused by shedding of the superficial skin flakes. This has been called **flaky-pain dermatosis**. Another similarly characteristic skin lesion of kwashiorkor is crazy-pavement dermatosis. Reticular pigmentation, mosaic dermatosis and pellagra-like lesions over the exposed parts (usually dorsal surfaces) may also be encountered (Figs 13.12 to 13.15).

Besides the aforesaid dermatosis, kwashiorkor children may suffer from indolent sores and ulcers besides superadded skin infections like pyoderma and scabies.

- **Gastrointestinal manifestations** include diarrhea, vomiting and anorexia. In spite of edema, the child may develop dehydration. Diarrhea may be due to



Fig. 13.14: Kwashiorkor in a toddler. Note the classical skin lesions and massive edema.



Fig. 13.15: Kwashiorkor. Typical crazy-pavement dermatosis and gross edema.

quite a few factors, including superadded infections and infestations and effect of malnutrition per se as already discussed.

- **Mineral and vitamin deficiencies** are common. Anemia is usually present and is moderate to severe in intensity. It is frequently iron-deficiency type though dimorphic and even pure megaloblastic morphology may be encountered. There is evidence that PEM may per se cause anemia. Accompanying factors such as intestinal parasitic infestations and systemic infections may also play a contributory role. Other mineral deficiencies are those of potassium and magnesium. Deficiency of vitamin A is frequent and may lead to serious problem of keratomalacia and irreversible blindness. Deficiencies of vitamin B-complex, C, D and E may also complicate the picture.
- **Hepatomegaly**, quite often fairly remarkable (liver may touch the umbilicus), is invariably present. The consistency is usually soft, the edge rounded and the surface smooth.
- **Superadded infections** (say, tuberculosis, broncho-pneumonia, enteritis, measles, pyoderma, etc.) and intestinal parasitic infestations (*Lambliia giardia*, *Entamoeba histolytica*, roundworm, hookworm, threadworm, *Hymenolepsis nana*, etc.) are common. Infection by Gram-negative organisms (usually enteritis and septicemia and occasionally urinary tract infection) is most troublesome to manage in such patients.
- **Clubbing** may be encountered in a proportion of the children with kwashiorkor as a result of the accompanying steatorrhea.
- **Nonspecific ECG changes** may be found in a small proportion of the cases. A significant cardiac involvement is seldom seen.

When kwashiorkor occurs in its full-blown picture, it is termed **florid kwashiorkor**. Box 13.9 shows grading of kwashiorkor in terms of severity.

Box 13.9 Grading of kwashiorkor

- **Grade I:** Pedal edema
- **Grade II:** Facial puffiness
- **Grade III:** Paraspinal and chest edema
- **Grade IV:** Ascites/anasarca.

Marasmus

(Nonedematous Malnutrition with Severe Wasting)

Though kwashiorkor has received far greater attention from the researchers, nutritional marasmus is encountered more frequently in several parts of the world, particularly in north India. At times, the condition is referred to as **atresia** or **infantile atrophy**.

Clinical Features (Figs 13.16 to 13.18)

Nutritional marasmus occurs usually in subjects less than three years of age; the peak incidence is seen during the first year of life. The disease may be encountered in later childhood.

A characteristic feature of the clinical picture is remarkable wasting of both muscles and subcutaneous fat. The face is wizened and shriveled—just as in the case of a monkey. In the early stages, the child is irritable, hungry and craves for food. However, in the later stages, he may become miserable and apathetic, refusing to take anything. Edema is conspicuous by its absence. Significant hair changes, dermatosis and marked fatty liver are also absent. As in kwashiorkor, diarrhea, mineral and vitamin deficiencies, superadded infections and parasitic infestation are commonly seen. Table 13.4 provides grading of nutritional marasmus.

Biochemical Changes

These are slight until marasmus is of very advanced degree. The reason is that the amino acids liberated from child's



Fig. 13.16: Marasmus. Note the remarkable wasting of both muscles and subcutaneous adiposity. The child had been on only highly diluted formula.



Fig. 13.17: Marasmus. Note remarkable wasting over gluteal region. This is the same marasmic child as in Figure 13.16.



Fig. 13.18: Marasmus. This is an example of PEM secondary to tuberculosis.

Table 13.4: Achar's grading of nutritional marasmus

Grades	Characteristics
1	Loss of fat from axilla/groin
2	Loss of fat from abdominal wall and gluteal region
3	Loss of fat from chest wall and back (paraspinal region)
4	Loss of buccal pad of fat (which consists of fatty acids); it takes longer time to disappear

own tissues make possible a continuing synthesis of serum enzymes, albumin and other essential metabolites.

- Anemia is mild to moderate and may be of any morphologic type though iron deficiency anemia undoubtedly dominates the picture.
- Electrolyte disturbances may occur in the presence of diarrhea and vomiting.
- Blood urea is usually normal.
- Blood sugar slightly raised.
- Duodenal enzymes show little or no reduction.

Diagnosis

Dietetic history suggests inadequacy of both proteins and calories (carbohydrates) in child's intake in the recent past. The predominant lack is of calories. Diagnostic criteria may be essential and nonessential as outlined below:

Essential Feature (Minimal Diagnostic Criteria)

- Growth retardation as evidenced by marked loss of weight and subnormal height/length.
- Gross muscle as well as subcutaneous fat wasting.
- Absence of edema.

Nonessential Features

- **Hair changes** are usually not present.
- **Classical dermatosis** of kwashiorkor is not seen. However, indolent sores and ulcers as also superadded skin infections occur very frequently.

- **Gastrointestinal manifestations** like diarrhea and vomiting occur as in kwashiorkor. A marasmic child is, however, hungry rather than anorexic, though he may develop anorexia once marasmus has advanced to extreme degree.
- **Mineral and vitamin deficiencies** occur fairly commonly. Anemia is usually mild to moderate and may be of varied morphology. Potassium and magnesium deficiencies occur in patients with diarrhea and vomiting. Vitamin deficiencies occur relatively less often compared to kwashiorkor.
- Liver is rather shrunk which is in sharp contrast to the fatty, enlarged liver of kwashiorkor.
- **Superadded infections and infestations** are nearly as common as in kwashiorkor.
- **Psychomotor change** is usually in the form of irritability rather than listlessness. Advanced cases may, however, become apathetic as is seen in kwashiorkor.
- **Clubbing** may be seen in a proportion of marasmic children. It seems to be related to the accompanying steatorrhea.

Marasmic Kwashiorkor

Marasmic kwashiorkor refers to cases demonstrating a combination of features of kwashiorkor and marasmus. Presence of edema is essential for this diagnosis (Fig. 13.19). For instance, an established case of nutritional marasmus may be mistakenly initiated on a diet consisting of lots of calories, but very little proteins. Such a child is a candidate for developing hypoproteinemia and clinical edema. Remaining features of kwashiorkor may or may not be present.

Prekwashiorkor

Prekwashiorkor refers to a child who has quite poor nutritional status and certain other features of kwashiorkor such as hair changes minus edema. Such a child, unless



Fig. 13.19: Marasmic kwashiorkor. Note remarkable wasting with pedal edema.

taken care of at this very stage, may develop edema and other features of full-blown kwashiorkor. A comparison of important features of marasmus and kwashiorkor is presented in Table 13.5.

Nutritional Stunting

If PEM starts fairly early in life and goes on and on over a number of years without causing overt picture of kwashiorkor or marasmus, child's height as well as weight may be significantly low for his age. This is what has been termed **nutritional dwarfing** (Case 1).

Case 1

An apparently healthy-looking child, appearing aged four years, is brought to a physician for a trivial medical problem. His height is 99 cm and weight 18.5 kg. Naturally, the physician forms an impression that the nutritional status of the child, including height and weight, is good enough for the age of four years. Right at this stage, the mother reveals that the actual age of the child is eight years which indeed surprises the physician. The fact is that this child is quite stunted and underweight for his actual age.

Nutritional dwarfing is a common problem in developing countries, but cases are not as frequently detected. It seems to be a kind of adaptation to poor diet (not as grave as to cause frank kwashiorkor or nutritional marasmus) over a prolonged period. These children are generally less active and less lively. They are more prone to diarrhea, pneumonia, tuberculosis or other infections prevalent in the region.

COMPLICATIONS OF PEM

Serious complications of PEM are summarized in Table 13.6.

PRINCIPLES OF MANAGEMENT OF PEM

Domiciliary (Home) Management

Mild Moderate Malnutrition

Children with mild to moderate malnutrition are best managed in their own homes and kept under surveillance

so as to find out improvement or deterioration in their nutritional status. The parents of such children are educated about the inadequacy in child's intake and guided how to correct it. The stress should be on the locally available economic foods, including **Hyderabad mix** (Table 13.7) rather than on expensive tinned protein preparations which should be reserved for special situations only. The parents must be apprised of the value of carbohydrates and the rationale of giving liberal amounts of semisolids and solids. They must understand why only milk will not be enough for the growing child. There is evidence that domiciliary treatment brings about gratifying results.

- It reduces the unnecessary hospital load, is much less expensive, and, in addition, gives nutritional education to the family and the community.
- Ours as well as many other workers' experience indicates that malnutrition relapses only infrequently when moderate PEM is treated at home. On the contrary, incidence of recurrences in hospital treated cases is fairly high.
- The management at home has got to be supervised and monitored by weekly visits of paramedical (say an anganwadi worker), visits to a nearby nutrition rehabilitation center or outpatient department (OPD) of a health center/hospital.

A prerequisite to domiciliary treatment is absence of severe infection(s), fulminant gastroenteritis and electrolyte imbalance. Good weight gain, as judged from the growth chart, is by and large the best yardstick of adequacy of response to nutritional rehabilitation.

Uncomplicated Severe Acute Malnutrition (SAM)

WHO had earlier categorically recommended hospitalization in case of uncomplicated SAM as well. It has now advocated home treatment for this category since it is not feasible to offer them hospital treatment and they can be managed well in domiciliary settings. This is in keeping with the IAP guidelines (Box 13.9).

Management in Nutrition Rehabilitation Center (NRC)

This concept, originally started in Southern America, aims at offering nutritional rehabilitation for mild to moderate PEM as a compromise between domiciliary and hospital managements. It offers a meeting point between classical treatment and prevention, embracing the positive points of both hospital and home management.

Two types of NRCs are—(1) day care center and (2) residential center.

Day Care NRC

It consists of a room for children, a kitchen, an examination room and a teaching space. At least one good meal is provided to children. Around 20–40 malnourished children along with their mothers who are expected to involve themselves in various activities are taken care of. The center remains open from 8 am–6 pm daily.

Table 13.5: Kwashiorkor vs. marasmus—comparison of important features

Feature	Marasmus	Kwashiorkor	Special comment
Age	First 3 years; usually less than 1 year	1–5 years	No age is a bar in both cases.
Essential features			
Growth failure/retardation	Yes Severe (weight less than 60% of expected for age)	Yes Moderate (weight more than 60% of expected for age)	Growth retardation is evidenced by low weight and low length/height.
Muscle wasting	Remarkable (skin-bone appearance)	Less remarkable	In kwashiorkor, muscle wasting though severe is somewhat masked by edema.
Subcutaneous fat wasting	Remarkable	Some subcutaneous adiposity retained	
Psychomotor change	Irritable, alert	Listless, apathetic, disinterested in surroundings	
Edema	Absent	Hallmark	In marasmic kwashiorkor, edema is present.
Nonessential (variable) features			
Classical hair changes	Absent	Usually sparse, light-colored, easily-pluckable and brittle; infrequently flag sign	
Typical dermatosis	Absent	Often present	In marasmus, classical dermatosis (say flaky paint, crazy pavement) is absent. Other skin conditions such as pyoderma, impetigo or scabies may be present in both kwashiorkor and marasmus.
Diarrhea	Yes	Yes	Villous atrophy leading to malabsorption, among other factors contributes considerably to development of diarrhea in both. Magnitude of steatorrhea is far more in kwashiorkor than in marasmus.
Appetite	Initially good	Anorexic	Eventually with worsening of condition, marasmic child also becomes anorexic.
Anemia	Mild to moderate	Moderate to severe	
Superimposed infection(s)	Frequent	Common	
Serum proteins	Low	Very low, albumin less than 2.5 g%	
Liver	Shrunk	Enlarged due to fatty change	
Clubbing	Sometime present	Sometime present	Chronic steatorrhea and/or coexisting tuberculosis may be responsible for clubbing.
Electrocardiogram (ECG)	Low voltage	Low voltage	
Response to treatment	Early	Slow	

Residential NRC

This is a larger and more organized NRC with a house-mother as the fulltime head with responsibilities that include daily work schedule of the mothers, purchase of food, issuing the correct amount of food as decided by the nutritionist, and keeping stock and maintenance of cleanliness of the center. The supervisory staff is part time and includes a doctor, a medical assistant/nurse, a home economist/nutritionist, and an agriculture teacher/extension worker. The center is attached to a health center or the pediatric department of a teaching hospital, or an under five clinic. The criteria for admission to the NRC are:

- Children especially at risk.
- Children who fail to gain weight over a period of three months.
- Children who do not catch-up in growth after serious illness (measles, whooping cough and diarrhea).
- Failure to breastfeeding.
- Mothers and children who find it difficult to cope with their problems in spite of the health teaching they receive at the under five clinic.
- Twins and triplets.

The stress in the NRC is on nutrition and health education, household budget teaching, homecraft teaching and actual feeding, using locally available foodstuffs and local methods of cooking and preparation. The successful rehabilitation at the NRC must be followed up at home so that the knowledge acquired during stay at the center continues to be applied at home.

Hospital Management

Complicated severe acute malnutrition (SAM) needs to be managed in hospital in three phases as discussed under SAM.

Table 13.6: Serious complications of advanced PEM

Complication	Remarks
Superadded infections	Both overt and hidden: Septicemia, pneumonia, diarrhea, pyoderma, scabies, UTI, tuberculosis.
Dehydration and dyselectrolytemia	Usually complicating accompanying diarrhea, often with lactose intolerance.
Hypothermia	An unattended rectal temperature of less than 35°C may prove fatal, causing SIDS.
Hypoglycemia	It contributes to poor response to nutritional therapy and carries a poor prognosis.
CCF	It is usually precipitated by excessive intake of sodium and fluid or severe anemia. Since cardiac size is invariably small in PEM, even a normal sized heart in X-ray should arouse suspicion of CCF.
Anemia	Moderate to severe anemia may result from malnutrition as such or factors such as superadded infection(s), contributing to development of CCF.
Bleeding	DIC may complicate the clinical picture (Fig. 13.20).
SIDS	Sudden death 4–7 days after admission. Usually, the cause remains unclear.

Abbreviations: UTI, urinary tract infections; CCF, congestive cardiac failure; SIDS, sudden infant death syndrome; PEM, protein energy malnutrition; DIC, disseminated intravascular coagulation.



Fig. 13.20: Severe PEM. Note the complication of bleeding diathesis (purpura fulminans) from DIC. Superimposed sepsis is often coexisting in such a situation.

Table 13.7: Hyderabad protein-energy rich mixture for home treatment of PEM

Roasted whole wheat	40 g
Roasted Bengal gram	16 g
Roasted groundnut	10 g
Jaggery	20 g
Total	86 g providing 330 kcal and 11.3 g proteins

Box 13.9**Domiciliary (home) treatment of uncomplicated SAM as per IAP**

- **Diet:** Energy-dense therapeutic diet with low bulk in the initial phase which should be:
 - Home-based (prepared/modified from the family pot; indigenous RUTF)
 - Cost-effective, easily available and acceptable
 - Fed frequently (6–8 times/24 hours)
- **Supplements:** Micronutrient and minerals
- **Oral antibiotics:** Usually cotrimoxazole or ampicillin for 7 days
- **De-worming:** Single dose
- **Warming up:** Hypothermia prevented by maintaining environmental temperature and covering the child well, especially during night.
- **Immunization:** Routine
- Health education
- **Others:** Family and community participation, nutrition counseling and household food security, etc.

Severe Acute Malnutrition**Definition**

WHO and United Nations Children Emergency Fund (UNICEF) define SAM as presence of any one of the following features in children aged 6 months to 5 years:

- Weight for height/length less than -3 SD or Z scores of the median in the 2006–2007 WHO growth charts
- MUAC less than 115 mm (11.5 cm) in children between 1 and 5 years
- Bipedal edema
- Visible severe wasting.

Infants and children suffering from SAM are at high risk of complications which may terminate in death. SAM may further be categorized as uncomplicated or complicated.

Prevalence

Approximately 20 million children under 5 years of age have SAM. Most of them live in South Asia and sub-Saharan Africa. The mortality rate is 7.3–18.7% every year. This equates to one million child deaths every year due to SAM.

Back home in India, NFHS –3 conducted in 2005–2006 shows that 8.1 million children are suffering from SAM, causing 0.6 million deaths annually. It also contributes to 24.6 million disability adjusted life year (DALY) in a year.

Etiology

A detailed description of etiology is available at the outset of this very chapter. Suffice to say here that immediate determinants include LBW, illnesses such as diarrhea, pneumonia and measles and poor dietary intake. Three underlying household determinants that influence the immediate determinants are food, care and health. Basic determinants include low socioeconomic status, poor education status, cultural taboos, inadequacy of water and sanitation.

Diagnosis

Children with SAM can be identified by frontline community workers like anganwadi worker (AWW), accredited social health activists (ASHA) and auxiliary nurse midwife (ANM). Once the diagnosis of SAM is made, the child has

to be assessed by an integrated management of childhood illness (IMCI)/integrated management of neonatal and childhood (IMNCI) trained health worker and a decision regarding the type of care (whether the child requires in-patient care or can be managed on outpatient basis) has to be made.

Management

Treatment of malnutrition is increasingly being shifted from **facility based management** to **community based approach**. This decentralization aims to increase access to services promoting early presentation and compliance.

Children who have coexisting human immunodeficiency virus (HIV) and tuberculosis with SAM also need simultaneous antiretroviral therapy and pneumocystis carinii pneumonia (PCP) prophylaxis and anti-tuberculous therapy (ATT) for adequate response.

Uncomplicated SAM

A large chunk (85–90%) of children with SAM does not have complications. They can be managed at home or in the community. Appetite test is of value in deciding if the SAM in a particular child is complicated or uncomplicated. The test comprises of offering local therapeutic feed to the SAM child who should not have taken any feed in the preceding two hours. The amount consumed should be measured at the end of the test. For passing the test, the child should have consumed a minimum of 25 mL/kg. If the child fails the test, he is in need of hospital treatment. Failure of the test during the course of follow-up too is a pointer for transfer to facility-based inpatient care.

Complicated SAM

The objectives of facility based treatment in complicated SAM are:

- To manage the complications and reduce the mortality.
- To improve the physical and psychosocial growth of children with SAM.
- To educate the mothers and care givers about appropriate feeding of infants and young children.
- To identify any social factors that are involved in the causation of SAM.

The management of SAM is in 3 phases— stabilization, transition and rehabilitation.

1. **Stabilization:** In this phase, child is stabilized with treatment of acute complications and then initiated on F-75 diet. This phase lasts 1–2 days.
2. **Transition:** Child comes to this phase when he is active and alert, appetite returns; there is beginning of loss of edema, no nasogastric feeds, infusions and no severe medical problems. This phase lasts 2–3 days. There is transition from starter to catch-up diet.
3. **Rehabilitation:** Child enters this phase when he has reasonable appetite and finishes 90% of the feed, major reduction of edema and no other medical problem.
 - General principles for routine care (10 steps)
 - Emergency treatment of shock and severe anemia
 - Treatment of associated conditions.

Common Complications

- Hypothermia/sometime fever
- Hypoglycemia
- Persistent vomiting, diarrhea, severe dehydration
- Severe anemia
- Fulminant infection(s)
 - Severe lower respiratory tract infection (pneumonia)
 - Extensive superficial infection
- Lethargy, drowsiness, apathy, seizures.

Criteria for Admission

- SAM with complications
- Failed appetite test
- Child less than 6 months with SAM
- Presence of bilateral pitting edema +/- (edema +++ always needs inpatient care).

Laboratory Investigations

- Random blood sugar
- Hemoglobin
- Serum electrolytes
- Screening for infection:
 - Total and differential count, blood culture sensitivity
 - Urine routine and culture sensitivity
 - Chest X-ray
 - Mantoux
 - HIV after counseling, if suspected
- Any other specific test based on clinical presentation.

WHO Recommended Ten Steps of Management of SAM (Fig. 13.21)

WHO has recommended that SAM should be treated to major phases—namely stabilization and rehabilitation (Box 13.10).

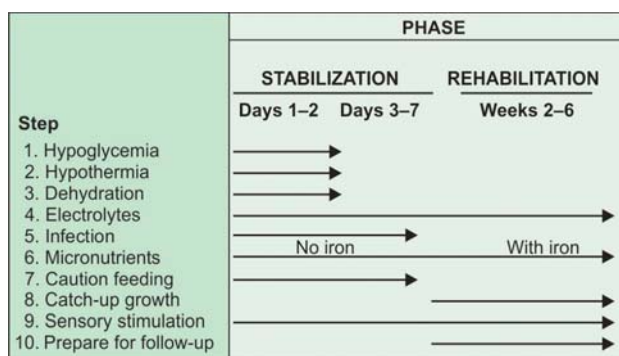


Fig. 13.21: WHO recommended 10 steps for management of SAM. Note the time frame for stabilization and rehabilitation.

Box 13.10 Two major phases needing management in SAM

1. **Stabilization phase:** Stabilization phase, comprising of first 7 days of hospital treatment is a spotlight on resuscitation (restoration of homeostasis) and treating complications such as hypothermia, hypoglycemia, dehydration and electrolyte imbalance, infections and heart failure, etc.
2. **Rehabilitation phase:** Here, spotlight is on building up the oral dietary intake over several weeks (say 2–6 weeks) in order to rebuild the wasted muscles and other tissues.

Abbreviation: SAM, severe acute malnutrition.

216 Step 1: Treatment and prevention of hypoglycemia

Hypoglycemia (blood glucose less than 54 mg/dL) is a very common problem in SAM. The following therapeutic/preventive measures are in order:

- If dextrostix less than 54 mg/dL, 50 mL of 10% dextrose or sucrose solution orally or through nasogastric tube depending on level of consciousness. If unconscious, convulsing or lethargic, 5 mL/kg of 10% glucose intravenous followed by the nasogastric feed should be given. Then therapeutic feeds (F-75) every half an hour for 2 hours should be given.
- A course of antibiotics.
- Feeds have to be given every 2 hourly during both day and night.
- Blood glucose has to be monitored.
- Prevention is by 2 hourly feeds including night feeds.

Step 2: Treatment and prevention of hypothermia

SAM infants and children are at risk of hypothermia, i.e. axillary temperature less than 35°C (95°F) or rectal less than 35.5°C (95.9°F), the risk being higher in marasmus.

The corrective/preventive measures are:

- Start feeds immediately. Give the feed every 2 hourly.
- Rewarm the child with warm blanket, heater or skin to skin contact.
- Treat hypoglycemia if present.
- Give first dose of antibiotics.
- Monitor temperature 2 hourly till temperature more than 36.5°C and every half hourly if using heater
- Severe hypothermia if temperature less than 32°C, in addition to the above give warm humidified oxygen, 5 mL/kg of 10% dextrose IV or 50 mL/kg of 10% dextrose by nasogastric tube and warm using overhead warmer, skin to skin contact and give warmed intravenous fluids.

Step 3: Treatment of dehydration without shock and with shock**(Without Shock)**

- Give ReSoMal (reduced osmolarity oral rehydration solution {ORS}) 5 mL/kg every 30 min for 2 hours, then 5–10 mL/kg every 2 hours for upto 10 hours alternating with starter diet.
- Monitor respiratory rate, pulse rate, urine frequency, stool/vomit frequency and signs of hydration every half hourly for the first 2 hours and then hourly.

(With Shock)

- Give humidified oxygen.
- Give 5 mL/kg of 10% dextrose intravenous and treat hypothermia if present.
- Give 15 mL/kg over 1 hour of Ringer's lactate or ½ normal saline in 5% dextrose. If improvement is present repeat another 15 mL/kg over 1 hour and then give 10 mL/kg/hr of ORS orally or nasogastric feed for 10 hours.
- If it fails to show improvement, treat as septic shock with antibiotics and dopamine.

Box 13.11**Recommended antibiotics and duration of antibiotic therapy in SAM**

- **Complicated SAM:** Ampicillin and gentamicin for 7 days with cloxacillin (if *Staphylococcus aureus* is suspected).
- **Septic shock:** Cefotaxim/ceftriaxone along with gentamicin.
- **Suspected meningitis:** Cefotaxim/ceftriaxone along with amikacin.
- **Dysentery:** Ciprofloxacin/ceftriaxone.

Duration of treatment

- **Clinical sepsis:** 7 days, UTI: 7–10 days
- **Culture positive sepsis:** 10–14 days
- **Meningitis:** 14–21 days, arthritis and osteomyelitis: 4 weeks
- **Uncomplicated SAM:** Oral amoxycillin 15 mg/kg 8 hourly for 5 days.

Abbreviations: SAM, severe acute malnutrition; UTI, urinary tract infection.

Step 4: Correction of electrolyte imbalance

Whereas body sodium in SAM is high, potassium and magnesium are quite low, warranting supplementation.

- Supplement potassium at 3–4 mEq/kg/day for 2 weeks.
- On first day give 0.3 mL/kg of 50% magnesium sulphate IM once and then 0.4–0.6 mmol/kg/day oral for 2 weeks.

It is important not to give any added salt in the diet since there is already excess of it in the body. Further hike in already high sodium may predispose to heart failure.

Step 5: Treatment and prevention of infection

Notwithstanding absence of overt signs such as fever, children with SAM have a high prevalence of infections which may well be predominantly Gram-negative. Antibiotics are recommended for overt and even hidden infection (Box 13.11).

Step 6: Correction of micronutrient deficiencies (micronutrient supplements)

The following supplementation is important:

- **Vitamin A:** On day 1, 2 and after 2 weeks. Multivitamin supplementation with vitamin A, C, D, E and B₁₂ in twice the recommended dietary allowance (RDA)
- **Folic acid:** 5 mg on 1st day and then 1 mg/day
- **Elemental zinc:** 2 mg/kg/day
- **Copper:** 0.2–0.3 mg/kg/day
- **Iron:** 3 mg/kg/day once child is in rehabilitation phase, i.e. after one week of hospitalization when resuscitation/stabilization phase is over and the child is having return of appetite and gaining weight. Initially, it is best avoided in the wake of risk of free radical generation and promotion of bacterial proliferation.

In the event of severe anemia, especially if complicated by respiratory distress, a whole blood transfusion (10 mL/kg) preceded by furosemide should be given slowly spread over 3–4 hour period, provided that the child is not having heart failure. In case of presence of heart failure, whole blood should not be given. Instead packed cell transfusion should be given.

Step 7: Initiation of refeeding

It is important to restart feeding as early as workable.

- **Infants less than 6 months:** Breastfeeding should be reinitiated or continued. If neither is possible, start non cereal starter feeds. When starting catch-up diet, it has

to be diluted by extra one third water to make 135 mL instead of 100 mL.

- **Supplementary suckling technique:** This can be practiced to enhance breastfeeding till lactation is established. In this technique, the baby while feeding at the breast will also be simultaneously sucking at a nasogastric tube, the end of which will be put in a cup with supplemental milk. The cup is initially placed 5–10 cms below the level of the nipple to help the weak infant suck, and gradually lowered down to 30 cms.
- **Infants more than 6 months and children:** Feeding should be initiated with therapeutic starter F-75 feeds (Table 13.8) in the acute phase and F-100/RUTF in the recovery phase. If child is taking less than 80% of the feed offered, nasogastric feeding should be given.

Feeding in stabilization phase aims at giving just sufficient calories and proteins to maintain the basic physiologic process. Small frequent feeds should be given orally or by the nasogastric tube. A total of 100 kcal/kg/day along with 1–1.5 g/kg/day of proteins and 130 mL/kg/day of fluids (in case of severe edema restrict to 100 mL/kg/day).

Step 8: Achieving catch-up growth

When child's appetite is back and he begins accepting increasing feeds, starter F-100 no longer meets with the child's enhancing requirements. It needs to be gradually replaced with F-100 diets, i.e. feeds with higher energy density (100 kcal/100 mL) and 2.5–3.0 g protein/100 mL (Table 13.8). Gradually, in increments, the volume of F-100 diet should be increased until he receives 200 mL/kg/day and 4–6 g/kg/day protein. Simultaneously, frequency needs to come down to 6 feeds/day. All this has to be on top of breastfeeding.

Step 9: Provision of sensory stimulation and emotional support

It is important to provide a holistic, cheerful and stimulating environment for proper cognitive and behavioral development during the course of nutritional therapy and rehabilitation. Structured play therapy over 10–30 min should be a routine for these children.

Table 13.8: Composition of starter F-75 and F-100 diets

Constituent	F-75 amount/100 mL	F-100 amount/100 mL
Energy	70 kcal	100 kcal
Protein	0.9 g	2.9 g
Lactose	1.3 g	4.2 g
Potassium	3.6 mmol	5.9 mmol
Sodium	0.6 mmol	1.9 mmol
Magnesium	0.43 mmol	0.73 mmol
Zinc	2.0 mg	2.3 mg
Copper	0.25 mg	0.925 mg
Percentage of energy from		
Protein	5%	12%
Fat	32%	53%
Osmolarity	333 mOsmol/L	419 mOsmol/L

Step 10: Preparation for follow-up after recovery

At the point when the child's weight for height (not weight for age which is bound to be low because of stunting) touches 90% of the expected and he is edema free, he is considered to have recovered.

- **Feeding in rehabilitation phase:** While changing to catch-up diet; for 2 days the starter diet is replaced with catch-up diet in the same amount. Subsequently, each feed is increased by 10 mL till some amount remains left over. A total of 8 feeds are given each day. Child's weight should be monitored regularly. The parent or the care giver has to be trained and counseled about breastfeeding, appropriate supplementary feeds, maintenance of hygiene and immunization during the hospital stay.
- **Structured play therapy** and loving care for emotional, physical and mental stimulation have to be provided. The child should be encouraged to spend time with his mother and other children on large play mats. Language and motor activities should be included in each play session. Children receiving psychosocial stimulation have better mental development and weight gain compared to those without stimulation.

Treatment of SAM in HIV and Tuberculosis Children

Antiretroviral therapy (ART) should be started 2 weeks after starting treatment of SAM once the recovery phase is well established. Amoxicillin should be given in addition to cotrimoxazole for PCP prophylaxis in children with HIV. National guidelines for treatment of HIV and tuberculosis should be followed.

Criteria for Discharge

These are listed in Box 13.12. A 15% weight gain has been recommended as the discharge criteria. If weight for height has to be used, a discharge at –1SD is recommended.

The discharge criteria, using the weight once edema has disappeared, should be taken for those admitted with edematous malnutrition. Once edema has subsided, if the weight for height and MUAC is already above –3SD and 11.5 cms respectively, the child should be discharged after 2 weeks to prevent relapse.

Treatment Outcome

- **Primary failure:** Non responder, i.e. no weight gain for 3 weeks or weight loss over 14 days.

Box 13.12 Criteria for discharge of SAM patients

- Weight for height more than –2 Z score of WHO growth chart
- MUAC more than 12.5 cm
- Absence of edema
- Good appetite (at least 120–130 kcal/kg/day)
- 15% weight gain and has consistent weight gain (5g/kg/day) on 3 consecutive days
- Complications have been treated
- Immunization is completed
- Child has received micronutrients
- Caregiver trained and motivated to provide care.

Abbreviations: SAM, severe acute malnutrition; WHO, World Health Organization; MUAC, mid-upper arm circumference.

Box 13.13**Factors contributing to poor response to nutritional rehabilitation**

- **Feeding inadequacy**—faulty and inadequate.
- Failure to adequately treat the accompanying infection(s) (pneumonia, diarrhea, UTI, AOM, intestinal parasitosis, malaria, tuberculosis, HIV).
- Failure to properly treat accompanying dehydration and dyselec-trolytemia.
- Failure to attend to accompanying deficiencies (say anemia)
- **Poor facilities**—untrained and poorly motivated staff, inadequate environment.
- **Serious underlying diseases**—malabsorption, immunodeficiency, inborn errors of metabolism, malignancy.

Abbreviations: UTI, urinary tract infection; AOM, acute otitis media; HIV, human immunodeficiency virus.

Box 13.14**Activities helpful in preventing SAM**

- Promotion of exclusive breastfeeding till 6 months of age
- Promotion of continued breastfeeding till 2 years
- Improving complementary feeding for children from 6 months to 2 years
- Improving maternal nutrition and education
- Improving availability of high quality food
- Improving access to health care
- Improving sanitation and hygiene.

- **Secondary failure:** Relapse—failed appetite test or 5% weight loss.
 - **Defaulter:** Not traceable for two visits.
- Factors contributing to poor response are listed in Box 13.13.

Prevention

Promotion of appropriate infant and young child feeding practices and knowledge among caregivers goes a long way in preventing SAM (Box 13.14).

Community Based Therapeutic Care (CTC)

Community based therapeutic care (CTC), a new concept for managing SAM is aimed at reducing the cost of treatment to the families as well as increasing the access to treatment. Its components are:

- **Community mobilization** to encourage early presentation and compliance.
- **Supplementary feeding protocols** for moderate acute malnutrition with no medical complications through outpatient therapeutic program (OTP) centers.
- **Therapeutic feeding protocols** for SAM with no medical complications through OTP centers.
- **Inpatient protocols** for SAM with medical complications. The OTP center essentially provides the following:
 - Provision of medical nutrition therapy.
 - Course of oral antibiotics along with vitamin A, folic acid, antihelminthics and antimalarials, when indicated.
 - Follow-up weekly/fortnightly by skilled health worker including provision of next supply of RUTF.

The principle of **continuum of care** from home and community to the health center and back, is critical for

Table 13.9: Recommended type of treatment for different types of SAM as well MAM

Type of acute malnutrition	Treatment recommended
SAM with complications	Phase I treatment as inpatient at stabilization center where the treatment is on standard guidelines for complicated SAM.
SAM without complications	Home-based treatment and rehabilitation employing RUTF which is supplied on a weekly or fortnightly basis as OTP.
MAM without complications	SFP in which the family is encouraged to take home ration for the malnourished child without complications.

Abbreviations: SAM, severe acute malnutrition; OTP, outpatient therapeutic program; SFP, supplementary feeding program; RUTF, ready to use therapeutic food, MAM, moderate acute malnutrition.

an effective management of SAM. A widely implemented community based approach along with facility based management for the complicated cases can go a long way in reducing the burden of deaths due to SAM.

Table 13.9 lists the type of treatment that should be given for different types of SAM as well as moderate acute malnutrition (MAM).

READY TO USE THERAPEUTIC FOOD (RUTF)**Background**

Therapeutic diet is recommended by the WHO after stabilization in SAM, F-100, is vulnerable to bacterial contamination and has to be used within few hours of preparation. This prevents it from being used on a large scale at the community level. This paved the way for the RUTF which was developed in the mid 1990s.

RUTF as Medical Nutrition Therapy

The RUTF is a medical nutrition therapy (MNT) with a balanced composition of type I and II nutrients based on sound scientific principles. They are soft crushable ready to use foods, which are energy dense and enriched with minerals and vitamins. It can be consumed without the addition of water. RUTF nutrient composition is similar to F-100, but with a greater energy and nutrient density. It also contains iron and is oil based with an extremely low water activity.

As RUTF does not contain water, it has lesser chances of getting contaminated and can be used at home without refrigeration. As it need not be cooked, there is no loss of heat labile vitamins.

Since RUTF does not contain water, plenty of safe drinking water has to be supplemented. Breastfeeding has to be continued along with RUTF.

RUTF is to be used only as a therapeutic feed for children more than 6 months and for a limited period (4–8 weeks) till the child recovers from SAM. Its use as a supplementary feed should be avoided. The amount of RUTF or any therapeutic feed to be consumed each day is given in Table 13.9.

RUTF has a higher success rate compared to RUTF free regimens in SAM. RUTF has also been shown to be better than F-100 in terms of weight gain, energy intake and time to recovery. The experience with of RUTF in SAM in few states of India has proved gratifying. The cost of production is about 3 USD per kg. Each child needs around 10–15 kg of RUTF over a period of 6–8 weeks during treatment.

PHENOMENA ENCOUNTERED DURING NUTRITIONAL REHABILITATION

Favorable

- Resumption of alertness as shown by a smile and interaction with mother
- Initiation of weight gain
- Disappearance of edema (by 7–10 post-therapy day)
- Disappearance of enteropathy and hepatomegaly
- Elevation of serum protein
- Attainment of normal weight for height in 1–3 months (*clinical recovery*).

Unfavorable

Refeeding Edema

Some infants and children with marasmus may develop edema following some correction in their nutrition. The so-called **refeeding edema** results from hyperinsulinemia causing decrease in sodium excretion. It may also follow nutritional rehabilitation with a diet that is predominant in calories (energy) with relative inadequacy of proteins.

Pseudotumor Cerebri

Overenergetic nutritional correction in malnourished infants may be accompanied by a transient rise of intracranial tension. The phenomenon is benign and self-limiting.

Nutritional Recovery Syndrome (Gomez Syndrome)

The term refers to interesting sequelae of events seen in children who are being treated with very high quantity of proteins during the course of rehabilitation from gross malnutrition. The syndrome is characterized by increasing hepatomegaly, abdominal distention, ascites, prominent thoracoabdominal venous network, hypertrichosis, parotid swelling, gynecomastia and eosinophilia. In some instances, splenomegaly also occurs. Though the syndrome was initially described in kwashiorkor from Africa, we have recorded its occurrence in both kwashiorkor and marasmus in India.

Etiopathogenesis

The etiopathogenesis of this syndrome remains speculative. Its development may well be related to endocrinal disturbances. That in PEM the function of the pituitary and its target glands is set at a lower ebb is well known. This response of the pituitary to the state of poor dietary intake appears to be an adaptive mechanism that permits survival of the patient by reducing body activity and metabolic rate, and by retarding growth. During nutritional rehabilitation, the greater utilization of the hormone by the body stimulates the pituitary to produce its trophic hormones. This results

in a response by the target glands. Thus, it appears that the nutritional recovery syndrome is caused by an increase in estrogen level and by a variety of trophic hormones produced by the recovering pituitary gland.

Encephalitis-like Syndrome

- **Progressive deterioration in sensorium:** About one-fifth children with kwashiorkor become drowsy within 3–4 days after initiation of dietary therapy. Most often, the condition is self-limiting. Occasionally, it may be accompanied by progressive unconsciousness with fatal outcome.
- **Kahn syndrome:** Even more rarely, a transient syndrome marked by coarse tremors, Parkinsonian rigidity, bradykinesia and myoclonus (Kahn syndrome) may appear six to several days after starting the dietary rehabilitation.
- **Tremors during recovery (kwashi-shakes):** Sometimes, tremors (the so-called *kwashi-shakes*) may occur during the recovery phase and may take even months to resolve. These encephalitis-like states are considered to be the result of far too much of proteins in the diet.

Refeeding Syndrome

It denotes fluid and electrolyte disturbances, especially severe hypophosphatemia, with neurologic, pulmonary, cardiac, neuromuscular, and hematologic complications (Box 13.15) following rapid overloading with too much of energy (calories) during nutritional rehabilitation. Associated hypokalemia and hypomagnesemia may cause cardiac arrhythmias which may prove fatal.

Etiopathogenesis

During prolonged fasting, the body aims to conserve muscle and protein breakdown by switching to ketone bodies derived from fatty acids as the main energy source. The liver decreases its rate of gluconeogenesis thus conserving muscle and protein. Many intracellular minerals become severely depleted during this period, although serum levels remain normal. Importantly, insulin secretion is suppressed in this fasted state and glucagon secretion is increased.

During refeeding, insulin secretion resumes in response to increased blood sugar, resulting in increased glycogen, fat and protein synthesis. This process requires phosphates, magnesium and potassium which are already depleted and the stores rapidly become used up. Formation of phosphorylated carbohydrate compounds in the liver and skeletal muscle depletes intracellular adenosine triphosphate (ATP) and 2,3-diphosphoglycerate in red

Box 13.15 Clinical manifestations of severe hypophosphatemia in refeeding syndrome

- **Neurologic:** Weakness, lethargy, paresthesia, disorientation, seizures and coma
- **Pulmonary:** Impaired contractility of diaphragm, dyspnea and respiratory failure
- **Cardiac:** Hypotension and poor stroke volume
- **Hematologic:** Leukocyte dysfunction, hemolysis and thrombocytopenia
- **Neuromuscular:** Areflexic paralysis.

220 blood cells, leading to cellular dysfunction and inadequate oxygen delivery to the body's organs. Refeeding increases the basal metabolic rate. Intracellular movement of electrolytes occurs along with a fall in the serum electrolytes, including phosphate, potassium and magnesium. Glucose, and levels of the B vitamin thiamine may also fall.

Cardiac arrhythmias are the most common cause of death from refeeding syndrome, with other significant risks including confusion, coma, convulsions and cardiac failure.

Prevention and Treatment

Too rapid nutritional correction with too much of carbohydrate diet should be avoided. Secondly, it is advisable to monitor phosphate levels during refeeding. Low phosphate levels (less than 1–1.5 mg/dL) are an indication for IV administration of phosphate, 0.08–0.16 mmol/kg over 6 hour.

Rickets

During nutritional recovery, as a result of rapid growth, vitamin D, calcium and phosphate consumption may fall short of the body needs, causing rickets. In some children, the pre-existing, but hidden rickets become manifest following restoration of bone growth during nutritional rehabilitation.

Anemia/Micronutrient Deficiency

In addition to the pre-existing anemia as a part of malnutrition, the child may manifest further worsening in hemoglobin status if iron and folic acid supplements are not provided during nutritional rehabilitation. Likewise, deficiencies of other micronutrients may become evident.

PROGNOSIS IN PEM

With good hospital care, mortality rate in gross PEM has today considerably fallen. Against the alarmingly high figures of 20–50% in the older series, the recent reports indicate around 10% mortality.

Bad prognostic signs include severe dehydration, hypoglycemia, hypothermia, CCF, superimposed infections, xerophthalmia, bleeding diathesis, hepatic dysfunction, seizures, significant change in sensorium and cachexia (extreme weight loss).

The causes of mortality include dehydration and electrolyte imbalance (dyselectrolytemia), hypoglycemia, hypothermia, fulminant systemic infections and CCF. In our experience, dehydration and electrolyte imbalance due to diarrheal disease and fulminant systemic infections are the chief killers of malnourished children. CCF, though uncommon, carries a very bad prognosis. In some cases hypoglycemia and hypothermia may prove fatal.

LONG-TERM SEQUELAE OF PEM

Growth Retardation

Infants who suffer from significant malnutrition fairly early in life and over a prolonged period develop a permanent and irreversible stunting of growth.

Mental Impairment

Now a sort of consensus seems to have emerged concluding that IUGR and malnutrition in the first year of life, if severe enough to retard physical growth and to warrant hospitalization, may cause retardation in mental performance, eventually leading to low intelligence and impaired learning skills.

Malnutrition and Liver

It is no longer believed that PEM causes cirrhosis in the long run. The concept is based on longitudinal follow-up studies of children suffering from severe PEM and the observation that incidence of cirrhosis in Africa, the home of kwashiorkor, is fairly low.

PREVENTION OF MALNUTRITION

At Family Level

The most significant in the preventive measures at family level is what is called **nutritional education**. Nutritional education consists of:

- Good antenatal care so that mother's own nutrition remains up to the mark and she does not develop malnutrition and anemia. This will be of much help in reducing the incidence of intrauterine growth retardation and LBW, the predecessors of malnourished children in very many instances.
- Encouragement to the mothers to breastfeed the infants for as long as they can. Even if the mother is not in a position to breastfeed the infant for some reason, it is of advantage to express her milk and feed it to him. Of course, she must take good diet and adequate amounts of fluids to maintain her lactation. In case of prolonged breastfeeding, it is to be confirmed that the lactation performance of the mother is adequate. Else, adequate supplementation of feeding becomes imperative.
- At the age of 6 months, the infant should start receiving complementary feeding, in addition to breastfeeding. The supplements should be combination of cereals, protein-rich foods and fruits such as mashed banana.
- The practice of shifting to artificial feeding in the form of bottle feeding with diluted cow milk or tinned milk should be discouraged, particularly in the poor in whose families it is virtually impossible to prevent occurrence of contamination of the bottle and the formula.

At Community Level

Here again nutritional education is of vital importance. Its delivery may be either through mass media such as radio, television, posters, documentary and films, etc. or imparting knowledge to the mothers at group meetings or at the doorstep of the family by the health auxiliary.

Secondly, surveys to detect cases of mild to moderate malnutrition, using preferably age-independent criteria, should be conducted. Such children may be kept under surveillance and, if required, given nutritional supplements.

The supplementary feeding programs in India include applied nutrition program, midday meal program for school children, special nutritional program, vitamin A prophylaxis program, anemia prophylaxis program, integrated child development services (ICDS), food for work program, etc. The principal beneficiaries of programs such are the nutritionally vulnerable preschoolers, school-going children and pregnant and lactating mothers. Ample evidence is now available to support the contention that adequate supplementation through the feeding programs results in improvement of nutritional status of the target population, provided that operational efficiency is ensured.

At National Level

This consists of measures to improve food production, control price-rise, make available cheap supplementary foods, fortify and enrich foods, prevent adulteration and irradiate certain foods such as wheat, potato and onion. Also, nutrition education and containment of population explosion are of paramount importance.

At World Level

Efforts to intensify various international food programs like those of:

- World Health Organization (WHO),
- Food and Agriculture Organization (FAO),
- United Nation Children's Emergency Fund (UNICEF),
- Cooperative for Assistance and Relief Everywhere (CARE),
- Oxford Committee for Famine Relief,
- Sub-Saharan International Development Organizations (SIDO)
- Danish International Development Agency (DANIDA),
- Indo-Dutch, etc.

NATIONAL NUTRITION PROGRAMS

Applied Nutrition Program

It was launched in 1963 with the assistance of UNICEF, WHO and FAO; this program aims at improving the nutritional status of the mothers (both expectant and nursing) as well as the infants and children. The cornerstone of the program is health education. The community is educated through personnel such as rural health workers, teachers, doctors, youth and women leaders to produce more of protective foods (say, fish, eggs, milk, vegetables and fruits) and to promote their consumption by the mothers and children.

The program covers 1,375 community development blocks, serving 1.7 million people. Ever since it was first launched, the program has not proved of as considerable value as was expected.

Special Nutrition Program (SNP)

This supplementary feeding program under the Ministry of Social and Welfare (Center) has been in operation ever since 1970. Its target population is preschool children (6 months–6 years) and expectant nursing mothers. In

the beginning, the program was restricted to urban slums and tribal areas, but later extended to selected rural and chronically famine-struck areas. **221**

Beneficiaries are provided 200 kcal and 8–10 g proteins per child per day up to one year of age and 300 kcal and 10–12 g proteins per day per child between ages 1 and 6 years. Beneficiary women receive daily 500 kcal and 25 g protein. The supplementary food is provided for 300 days in a year. On the spot provision of cooked food approach has been found to be in the greater interest of the child rather than the take-home ready-to-eat preparation approach. This program has attained coverage of several millions.

Midday Meal Program

It is also called **school lunch program**; it was first organized in 1957 in Tamil Nadu (then Madras State). Since 1962, it has been in operation in several parts of India and is at present estimated as covering around 16 million children.

The two major objectives of the program are—**first**, improvement in the nutritional status of the children since they are provided supplementary foods and are also given nutrition education; **second**, to provide a kind of incentive for enrollment and retention of children in the schools, thereby enhancing the literacy rate.

Based on the source of food material required to support the program, it has two components—**first** is the CARE assisted program which covers 11 million beneficiaries in 15 states/union territories. In this program, ready-to-eat foods, say muruku, are provided for about 200 days in a year to the school children. **second** program operates entirely at the expense of the State governments.

Since 1982, Tamil Nadu is financing a new nutritious meal program in over 21,000 balwadies and 32,000 primary schools for children between 2 and 10 years. As many as 28 recipes such as rice, dal, oil, and vegetables, are formulated for use. Each meal claims to supply 400 kcal and 10 g proteins for preschool child and 500 kcal and 12 g protein for the older child. Yet, the cost of the one meal remains as low as 45 paise.

Nutritional Anemia Prophylaxis Program

Children aged 1–5 years are given a daily tablet of 20 mg of elemental iron (ferrous sulfate 60 mg) plus 100 µg (0.1 mg) folic acid for 100 days. Mothers (both pregnant and nursing) are given a daily tablet of elemental iron 100 mg plus folic acid 0.5 mg for 100 days.

Supplementary Nutrition in ICDS

In this intersectoral program, supplementary nutrition for the child and mother is an important component. Children upto 6 years are provided 300 kcal and 8–10 g protein daily. Twice this quantity is provided to malnourished children. In case of pregnant and nursing mothers, 50–100 kcal and 20–25 g protein are provided as supplements.

222 Balwadi Nutrition Program

This program, first started in 1970, is under the overall charge of social and welfare department of the union government. The budget allocation at present is over 17 million. The supplement food given to the child provides 300 kcal and 10 g proteins per child.

Anemia Control Program

Iron and folic acid tablets are distributed to the pregnant women and young children through the maternal and child health centers in the towns and primary health centers in the rural areas. At present nearly 28 million women and children are benefiting from the program.

Nutritional Blindness Prevention Program

This program has been in operation since 1970 and consists of giving every six months a dose of 200,000 international units of vitamin A (one teaspoonful) to children in endemic areas. The practice is continued till the child crosses 5 years of age.

In areas where this program is operative, incidence of blindness due to vitamin A deficiency (VAD) has dramatically fallen.

Iodine Deficiency Control Program (Goiter Control Program)

This national program, in operation since 1962, aims at controlling endemic goiter (thyroid swelling, visible over the front of the neck) through supply of iodized common salt to the population in the endemic areas. Fortification of the salt is done in such a way that it does not affect the acceptability of the stuff. For more details, See Chapter 11 (Nutritional Requirements).

ICDS Scheme

This scheme aims at providing a package of services with the major objective of:

- Improvement of health and nutritional status of children below 6 years and ensuring their all round development
- Reduction of death and disease
- Assisting the mother to look after health and wellbeing of child by providing nutrition and health education.

The target beneficiaries of the scheme are children under 6 years and women between 15 and 44 years. The stress is on women who are expectant or nursing. For details, See Chapter 9 (Community Pediatrics).

NATIONAL NUTRITION POLICY

Acknowledging that malnutrition, especially in infants and children, in India is rampant, a National Nutrition Policy adopted in 1993 has been in operation.

Aims and Objectives

- To identify vulnerable groups requiring immediate intervention.

- To identify key areas for action in the field of food production, supply, information, nutrition education, rural development, health care, monitoring and surveillance.

National Plan of Action on Nutrition (NPAN)

- Reduction in moderate and severe malnutrition among preschool children by half.
- Reduction in incidence of LBW infants to less than 10%.
- Reduction in chronic undernutrition and stunted growth in children.
- Elimination of blindness due to VAD.
- Reduction in iron-deficiency anemia in pregnant women by 25%.
- Universal iodization of salt for reduction of iodine deficiency disorders (IDD) to 10%.
- Giving due emphasis to geriatric nutrition.
- Production of 250 million tonnes of food grains.
- Improving household food security through poverty alleviation programs.
- Promoting appropriate diets and healthy lifestyle.

The short and long-term measures to realize these goals are listed in Box 13.16 and 13.17 respectively.

Box 13.16 Short-term measures concerning NPAN

- Nutrition intervention for specially vulnerable groups in the form of:
 - Expanding the safety net, particularly ICDS program
 - Appropriate behavioral changes among mothers
 - Reaching the adolescent girls
 - Ensuring better coverage of expectant women for the better health and reducing the incidence of LBW infants.
- Fortification of essential foods with iron and iodine
- Popularization of low-cost nutritious foods
- Control of micronutrient deficiencies amongst vulnerable groups.

Abbreviations: NPAN, National Plan of Action and Nutrition; ICDS, integrated child development services; LBW, low birth weight.

Box 13.17 Long-term measures concerning NPAN

- Food security
- Improvement of dietary pattern through production and demonstration
- Policies for affecting income transfers by:
 - Improving the purchasing power, and
 - Streamlining the public distribution system
- Land reforms
- Health and family welfare
 - Food security
 - Improvement of dietary pattern through production and demonstration
 - Policies for affecting income transfers by:
 - Improving the purchasing power, and
 - Streamlining the public distribution system
 - Basic health and nutrition knowledge
 - Prevention of food adulteration
 - Nutrition surveillance
 - Monitoring of nutrition program
 - Research into various aspects of nutrition
 - Equal remuneration for men and women
 - Better communication strategies
 - Minimum wage administration
 - Community participation.

Abbreviation: NPAN, National Plan of Action and Nutrition.

OVERWEIGHT AND OBESITY

Overweight and obese children are a reflection of just the opposite of undernutrition. Despite overwhelming problem of nutritional deficiencies in resource-limited countries, nutritional obesity too is encountered, especially among the infants, children and adolescents of the elite who ape the lifestyle of the west.

Nutritional obesity is exogenous or constitutional in origin, usually as a result of overeating or poor expenditure on account of inactivity. It often runs in families, one or both

parents being obese. Unlike endogenous obesity from endocrinal or genetic causes, here obesity is generalized rather than central and growth/height velocity is accelerated rather than delayed. Dysmorphism, a common feature of genetic conditions associated with obesity is not present.

In India, it is a matter of concern since we already are in the thick of a struggle against undernutrition. Our problem is, therefore, the so-called **dual burden of under-nutrition**. The topic is discussed in details in Chapter 4 (Growth Disorders).

Multiple Choice Questions

- Spot the wrong observation:
 - Mild to moderate malnutrition which eventually ends up in stunted growth continues to exist in around 48% children in India
 - According to Gopalan's hypothesis, there is hardly any significant difference in the dietary background of children with kwashiorkor and marasmus
 - Hair and skin changes are essential for the diagnosis of kwashiorkor
 - Though marasmic children are hungry in the beginning, eventually they also develop anorexia
- Which of the following is not a feature of PEM?
 - Hyperkalemia
 - Hypernatremia
 - Hypoglycemia
 - Hypothermia
- Which one is the index of chronic malnutrition (nutritional stunting)?
 - Weight for age
 - Weight for height
 - Height for age
 - BMI
- All the following statements are correct, except:
 - According to Waterlow classification, height for age <85% of the standard points to severe stunting
 - According to Gomez classification, a weight between 75–90% of standard suggest mild malnutrition
 - Purpura fulminas is a common complication of PEM
 - Normally, hydroxyproline index varies between 2–5
- Favorable phenomena occurring during management of PEM include each of the following, except:
 - Resumption of alertness as shown by a smile and interaction with mother
 - Initiation of weight gain
 - Disappearance of edema (by 7–10 post-therapy day), disappearance of enteropathy and hepatomegaly and elevation of serum protein
 - Gomez syndrome

Answers

1. C 2. A 3. C 4. C 5. D

Clinical Problem-solving

Review 1

An 18-month-old girl suffering from SAM (weight 6 kg, MUAC 10.5 cm, obvious wasting) was stabilized according to the WHO-recommended schedule. On 5th day of initiation of hospitalization, her appetite showed considerable improvement so much and so that she began consuming around 1400 kcal/24 hours. Then, all of sudden, she developed arreflexia hypotonia, seizures, low blood pressure and breathlessness.

- What could be the cause of her acute deterioration?
- What is it?
- How does it develop?
- How to prevent it?

contd...

Review 2

A 3-year-old suffering from SAM (edematous), presents with cold clammy body (axillary temperature 34°C), blood glucose 40 mg/dL.

1. What is the diagnosis?
2. How shall you manage the complications?
3. If left untreated, what can be the consequences?
4. How can these complications be prevented?

Answers**Review 1**

1. Refeeding syndrome
2. It denotes fluid and electrolyte disturbances, especially severe hypophosphatemia, with neurologic, pulmonary, cardiac, neuromuscular, and hematologic complications following rapid overloading with too much of energy (calories) during nutritional rehabilitation. Associated hypokalemia and hypomagnesemia may cause hypokalemia and hypomagnesemia. The resultant cardiac arrhythmias prove fatal.
3. During severe starvation, as in SAM, ketone bodies become the main source of energy and many intracellular minerals get depleted. Insulin secretion gets suppressed. During overenergetic and too rapid nutritional rehabilitation employing predominantly carbohydrates, insulin secretion picks up in response to increasing blood sugar. This further depletes the intracellular minerals (phosphorous, magnesium and potassium), causing CNS, respiratory, cardiovascular manifestations. This seemingly happened in this child.
4. Too rapid nutritional correction with too much of carbohydrate diet should be avoided. Secondly, it is advisable to monitor phosphate levels during refeeding. Low phosphate levels (less than 1–1.5 mg/dL) are an indication for IV administration of phosphate, 0.08–0.16 mmol/kg over 6 hour.

Review 2

1. This child with kwashiorkor type of SAM is suffering from two major complications, namely hypothermia and hypoglycemia.
2. Start feeds immediately. Give the feed every 2 hourly.
Rewarm the child with warm blanket, heater or skin to skin contact.
Treat hypoglycemia if present.
Give first dose of antibiotics.
Monitor temperature 2 hourly till temperature more than 36.5°C and every half hourly if using heater.
Severe hypothermia if temperature less than 32°C, in addition to the above give warm humidified oxygen, skin to skin contact and give warmed intravenous fluid.
For associated hypoglycemia (blood glucose less than 54 mg/dL) 5 mL/kg of 10% dextrose IV or 50 mL/kg of 10% dextrose by nasogastric tube and warm using overhead warmer.
3. Prevention of hypoglycemia is by 2 hourly feeds, including night feeds.
4. Prevention of hypothermia is by keeping the SAM child warm through different means.

FURTHER READING**JOURNAL ARTICLES/BOOK CHAPTERS**

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INTRODUCTION

These organic compounds, though needed in only small amounts, are essential for maintenance of normal health and must be provided from external (usually dietary) sources. The functions are:

- **As hormones:** Vitamin D
- **As antioxidants:** Vitamin E
- **As regulators of tissue growth and differentiation:** Vitamin A
- **As coenzymes:** B complex vitamins, e.g. pyridoxine for nicotinic acid
- **For control of protein synthesis:** Vitamin A, D, E and K.

CLASSIFICATION

Two broad categories are:

1. **Water-soluble:** Vitamins B complex and C
2. **Fat-soluble:** Vitamins A, D, E and K.

Water-soluble vitamins are not stored in the body in any appreciable quantity. Their excessive consumption causes no particular toxicity, the surplus being excreted. On the contrary, fat-soluble vitamins are stored in liver. Their excessive consumption may, therefore, cause toxicity.

Vitamin deficiencies may occur as such or in combination with other nutritional problems such as protein energy malnutrition (PEM).

WATER-SOLUBLE VITAMINS

THIAMINE

(Vitamin B₁)

- **Functions:** It has a role in nerve conduction, as a coenzyme in transketolation and decarboxylation of alpha-ketoacids, in carbohydrate and protein metabolism.
- **Dietary source:** Milk, whole grain cereals, pulses, dried yeast, oilseeds, fruits and eggs. Green vegetables and meat are relatively poor in thiamine.
- **Daily requirement:** 0.4 mg/1000 kcal.

Deficiency

- **Etiology:** Thiamine deficiency occurs either because of poor intake in the diet, malabsorption states, or prolonged illness.
- **Clinical features:** Thiamine deficiency leads to the disease, *beriberi*. It occurs usually in infants (*wet beri-*

beri) though older infants and children may also suffer from its chronic form (*dry beriberi*). Meningitic form is also known.

The earliest symptoms occurring in early infancy (especially if the mother is providing thiamine-deficient breast milk), include restlessness, bouts of excessive crying (as if the infant is having an abdominal colic), vomiting, abdominal distention, flatulence, constipation and insomnia.

- In the **acute cardiac form** (wet beriberi), the infant may develop congestive cardiac failure in the form of tachycardia, gallop rhythm, dyspnea, cyanosis, hepatomegaly, cardiomegaly, edema and pulmonary edema. The possibility of thiamine deficiency should always be considered in endemic areas in subjects presenting with intractable congestive cardiac failure.
- In the **chronic neurologic form** (dry beriberi), the manifestations may include anorexia, weight loss, weakness, diarrhea, constipation and edema. The child is usually drowsy and apathetic. Ataxia is common. There may be peripheral neuritis and various palsies, including hoarseness due to vocal cord paralysis, and nystagmus. Deep tendon reflexes are usually absent.
- In the **meningitic form**, the clinical picture is dominated by bulging anterior fontanel, dilated pupils, head retraction and coma. Convulsions may occur, leading to a mistaken diagnosis of encephalitis or meningitis. Cerebrospinal fluid (CSF) reveals no abnormality.

In addition to all this, thiamine dependency has been incriminated in the etiology of:

- Anomalies of branched chain ketoacid decarboxylase system, e.g. maple syrup urine disease.
- Syndrome of optic atrophy, intermittent ataxia, lactic acidosis and hyperalaninemia due to pyruvate decarboxylase deficiency.

Differential Diagnosis

Differentiation needs to be made from pyloric stenosis and other high obstruction in the presence of troublesome vomiting. Endomyocardial fibroelastosis, congenital heart disease and glycogen storage disease involving the heart (Pompe disease) may be considered in the presence of congestive cardiac failure (CCF). Chronic neurologic form would require differentiation from lead poisoning. Menin-

226 gitic form may be confused with meningitis or encephalitis; a normal CSF may prove most helpful in such a situation.

Diagnosis

It is more or less clinical. However, if facilities are available, the following investigations may be done:

- **Blood thiamine level:** Less than 4 µg/dL (normal is 10 ± 5 µg/dL) is suggestive;
- **Milk thiamine level:** Less than 7 µg/dL;
- **Red cell transketolase level:** The level is low. A dramatic response, within a few hours, to an intramuscular injection of 25 mg of thiamine is a good therapeutic test.

Treatment

As soon as the diagnosis is convincingly made, the child must receive 10 mg of thiamine intravenously. In the subsequent three days, he should be given 10 mg of the vitamin intramuscularly twice daily. Over the next six weeks, 10 mg daily should be administered orally. The breastfeeding mother should receive thiamine therapy simultaneously.

Prognosis

It is excellent, provided reasonable intake of thiamine is ensured.

Prevention

Ensuring that at least 0.4 mg of thiamine is provided in the daily diet (thrice the quantity in case of pregnant and lactating women) prevents beriberi.

RIBOFLAVIN

(Vitamin B₂)

- **Function:** As a constituent of flavoprotein coenzymes (flavin adenine dinucleotide {FAD} and flavin mononucleotide {FMN}), it plays an important role in the intermediary metabolism of carbohydrates.
- **Dietary sources:** Both animal and vegetable foods such as liver, fish, egg, kidney, meat, beans, yeast, green leafy vegetables (GLV), cereals, legumes, groundnut and milk (5 times more in cow milk than in human milk).
- **Daily requirement:** 0.6 mg/1000 kcal.

Deficiency

Deficiencies of thiamine and riboflavin may be coexisting.

- **Etiology:** Since both breast milk and cow milk provide sufficient riboflavin for infant's needs, its deficiency usually occurs in children on restricted protein intakes or with dominant protein malabsorption states. Most subjects are vegetarian. Its deficiency may also occur in neonates under phototherapy because of its being subject to photodegradation.
- **Clinical features:** Manifestations include angular stomatitis (Fig. 14.1), cheilosis (fissuring of lips), nasolabial seborrhea and occasionally purplish-red (magenta) stomatitis with smooth tongue (Fig 14.2). There may occur corneal injection (vascularization) at the lim-



Fig. 14.1: Angular stomatitis and cheilosis from riboflavin (vitamin B₂) deficiency. Note the lesions at the corners of the mouth (angular stomatitis) along with fissuring of the adjoining lips (cheilosis). Most such patients are pure vegetarians.



Fig. 14.2: Glossitis with stomatitis from riboflavin deficiency. Note the typical smooth and magenta tongue. There is also an evidence of angular stomatitis.

bus, leading to excessive lacrimation, photophobia, eye pain and later interstitial keratitis.

Diagnosis

It is essentially clinical. Laboratory investigations include:

- Urinary excretion of riboflavin less than 30 µg/24 hours.
- Excretion of less than 125 µg of riboflavin/g of creatinine in a random urine sample.
- Increased erythrocyte glutathione reductase activity after the addition of FAD.

Treatment

Therapy consists of administering riboflavin, 3–10 mg orally or 2 mg intramuscularly daily for a few days. This should be followed by 10 mg orally daily for about three weeks. With this regimen, response is good. Complete recovery occurs provided that adequate intake of vitamin B₂ is ensured in the weeks and months ahead.

Prevention

In order to prevent riboflavin deficiency, it should be ensured that the daily diet provides at least 0.6 mg riboflavin per 1,000 kcal. It is advisable to administer supplements of riboflavin (the whole B-complex may be still better) to the infants and children belonging to vulnerable categories.

NICOTINIC ACID

(Niacin, Nicotinamide, Vitamin B₃)

- **Functions:** Nicotinic acid (niacin) or vitamin B₃ is also involved in the carbohydrate metabolism and plays a vital role in the functioning of the skin, gastrointestinal tract, central nervous system and hematopoietic system.
- **Dietary sources:** This vitamin may be obtained either from the natural food sources or from the tryptophan endogenously. The natural food sources include milk, liver, pork, fish, cheese, egg, yeast, cereals and vegetables, etc.
- **Daily requirement:** 6.6 mg/1000 kcal.

Deficiency

- **Etiology:** Nicotinic acid deficiency is usually encountered in children receiving a maize diet as staple, in chronic diarrhea, in malabsorption states, and in anorexic states. Pyridoxine deficiency may also contribute to nicotinic acid deficiency and pellagra-like lesions.
- **Clinical features:** Pellagra usually occurs in children of school-going age. The manifestations are briefed as **4Ds** (Dermatosis, Diarrhea, Dementia and Death).
 - The characteristic lesions are seen over the exposed areas of the skin, such as limbs, neck, (Casal necklace) and cheeks (Fig. 14.3). The lesions are symmetrical of desquamating pigmentary dermatitis type and are aggravated by sunlight.
 - Gastrointestinal symptoms in the form of red and sore tongue, dysphagia, nausea, vomiting and diarrhea.



Fig. 14.3: Pellagra. Note the characteristic skin lesion, especially necklace-like involvement of the neck.

- Dementia is encountered much less in childhood than in adults. Most children with pellagra are simply apathetic.
- Anemia as also other signs of malnutrition is usually present.

Diagnosis

It is purely clinical.

Differential Diagnosis

At times, severe PEM in the form of kwashiorkor may warrant differentiation. Remember that in kwashiorkor the skin lesions tend to be around pressure sites and flexure surfaces in the trunk, groin and knee rather than over the exposed parts as is typical of pellagra.

Treatment

Nicotinamide, 50–300 mg daily in divided doses orally, given for two weeks followed by adequate supply of B complex vitamins in diet brings about complete recovery.

Prevention

The disease may be prevented by providing a balanced diet containing 5–10 mg daily supply of nicotinamide.

PANTOTHENIC ACID

(Vitamin B₅)

It is synthesized by microbes from pantoic acid and β-alanine in addition to food sources.

- **Function:** It plays an important role in the synthesis of fatty acids, cholesterol and steroids, metabolism of pyruvate and alpha-ketoglutarate.
- **Dietary sources:** Almost all naturally occurring foods, especially germinated wheat; liver, dried yeast, egg yolk and fish.
- **Daily requirement**
 - **Infants:** 1.5–2.5 mg and 2–5 mg
 - **Children:** 5–8 mg
 - **Adolescents:** 10 mg.
- **Clinical uses:** Burning feet syndrome, hair loss, seborrhea, premature graying of hair, obesity and multiple sclerosis.

Deficiency

- **Etiology:** Usually in combination with other B complex deficiencies.
- **Clinical features:** Burning-feet syndrome, gastrointestinal tract (GIT) upset, sleep disturbances (especially insomnia), headache and muscle cramps.

Treatment

Calcium D-pantothenate 10–50 mg/day is suggested.

PYRIDOXINE

(Vitamin B₆)

- **Functions:** Vitamin B₆ plays a vital role in the metabolism of proteins and fatty acids. It is claimed to have a

228 role in blood formation, in proper functioning of the nervous system and in conversion of tryptophan to nicotinic acid.

- **Dietary sources:** Its natural sources include liver, egg yolk, meat, wheat germ, soyabeans, yeast, peas, pulses and cereals. It is found in only small quantity in most vegetables and milk.
- **Daily requirement:** 1–1.5 mg.

Deficiency

- **Etiology:** Pyridoxine deficiency of nutritional origin is rare in childhood—in fact, in humans as such. Deficiency may, however, complicate:
 - Prolonged isoniazid or cycloserine therapy in tuberculosis
 - Penicillamine therapy in Wilson disease
 - Use of contraceptives.

Pyridoxine-responsive convulsions and anemia have been described. Pyridoxine-dependent inborn errors of metabolism, e.g. homocystinuria, cystathioninuria, xanthurenic aciduria, kynureninase deficiency and hyperoxaluria, are also reported.

- **Clinical features:** Manifestations include:
 - Convulsions refractory to usual therapy
 - Microcytic-hypochromic anemia refractory to iron therapy
 - Growth retardation
 - Gastrointestinal symptoms like diarrhea
 - Seborrheic dermatitis around nose and eyes
 - Sensory neuropathy (uncommon in children)
 - Cheilosis and glossitis (infrequent in childhood).

Diagnosis

High index of suspicion of vitamin B₆ deficiency in infants with persistent convulsions, provided that hypoglycemia, hypocalcemia and birth injury have been excluded would help to diagnose this condition.

Such an infant should receive 50–100 mg of pyridoxine intravenously. If the response is gratifying, diagnosis is quite probable. The confirmation of diagnosis may be done by the tryptophan loading test. The same applies to anemia refractory to iron deficiency.

Treatment

Administration of 5 mg of pyridoxine intramuscularly followed by 0.5 mg daily orally for two weeks causes complete recovery.

Excess/Toxicity

Ataxia, stiffness in the feet followed by the cumbrous hands and night-time restlessness.

BIOTIN

A relatively less-understood vitamin, it is mainly produced by the gastrointestinal flora.

- **Functions:** Biotin acts as a coenzyme in carboxylation reactions (Box 14.1).

Box 14.1

Carboxylation reactions needing biotin as a coenzyme

- Acetyl-CoA carboxylase → malonyl-CoA in fatty acid synthesis.
- Pyruvate carboxylase → oxaloacetate in Krebs cycle.
- Propionyl-CoA carboxylase → in methylmalonyl-CoA in Krebs cycle.
- Methylcrotonyl-CoA carboxylase in catabolism of leucine.

- **Dietary sources:** Meat (especially liver), egg (yolk), milk and yeast extract.
- **Daily requirement:** 0.15 mg.

Deficiency

- **Etiology:** Most common cause is consumption of large number of raw eggs. The white (yolk) of egg is supposed to be rich in a glycoprotein, **avidin**. Avidin binds to biotin (avidin-biotin complex) so that its absorption is hindered. Prolonged parenteral nutrition (PN), without supplements of biotin may cause biotin deficiency. Infants of biotin-deficient mothers may develop biotin deficiency.
- **Clinical features:** These include anorexia, vomiting, pre-mature hair-fall, hyperkeratotic skin, glossitis, muscle pains, hyperesthesia, anemia, hyperlipidemia (hyper-cholesterolemia). Maternal deficiency may cause deficiency signs in infants and children and may even contribute to dysmorphism.

Treatment

- **Mild deficiency:** 2–5 mg/day (orally {O}) for 2–3 weeks.
- **Severe deficiency:** 200 µg/day parenterally for 2–5 days.

Prevention

Parenteral nutrition given over a prolonged time should have biotin incorporated.

VITAMIN B12

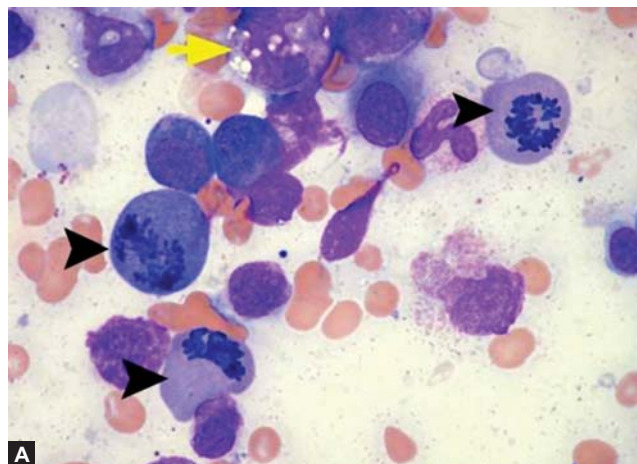
(Cyanocobalamin, Extrinsic Factor of Castle)

Cyanocobalamin is primarily produced by intestinal microbial flora.

- **Functions:** It is a coenzyme for conversion of homocysteine into methionine and L-methylmalonyl-CoA to succinyl-CoA for important metabolic reactions and synthesis of deoxyribonucleic acid (DNA) in bone marrow.
- **Dietary sources:** Animal origin foods such as meat (richest source is liver), fish, eggs; fresh milk and cheese milk powders.
- **Daily requirement**
 - **Infants:** 0.3 µg
 - **Children:** 1 µg
 - **Adolescents:** 1.5–2 µg.

Deficiency

- **Etiology:** Strict vegetarianism; malabsorption syndrome (especially endemic tropical sprue, blind loop syndrome, inflammatory bowel disease), infantile



Figs 14.4A and B: Vitamin B₁₂ deficiency. (A) Note the megaloblastosis in the bone marrow of a child suffering from vitamin B₁₂ deficiency as a part of endemic tropical sprue. Besides manifestations of malabsorption, he had skin pigmentation; (B) Note the pigmentation of skin, including soles.

tremor syndrome; drugs like neomycin, colchicine, para-amino salicylic acid (PAS) deficiency of intrinsic factor (pernicious anemia).

- **Clinical features:** Megaloblastic anemia (Fig. 14.4A) manifesting with pallor, skin pigmentation (Fig. 14.4B), smooth, red and painful tongue, neurologic manifestations (ataxia, paresthesias, hyporeflexia, tremors, peripheral neuropathy, subacute combined degeneration) and depression, etc.

Diagnosis

- Macrocytic/megaloblastic erythropoiesis
- Serum B₁₂ level less than 100 µg/mL with increased level of serum lactic acid dehydrogenase (LDH)
- Methyl malonic aciduria is a sensitive and reliable index
- Schilling test.

Treatment

- For megaloblastic anemia, Vitamin B₁₂ 1 mg (1000 µg) intramuscular (IM) leads to prompt hematological response (reticulocytosis) in 2–4 days.
- For neurologic involvement, same IM dose should be repeated daily for two weeks followed by a monthly maintenance dose (same dose and again IM) throughout life.

FOLIC ACID

(Folacin, Folate)

- **Functions:** Essential for maturation of red blood cells (RBCs). Moreover, it assists in protecting DNA and ensuring its replication when under attack by free radicals.
- **Dietary sources:** Meat (liver, kidney), egg, yeast, GLVs (spinach, cabbage, turnip greens), asparagus, mushrooms, beans, peas, sunflower seeds, whole grains.
- **Daily requirements**
 - **Infancy:** 40 µg

- **Children:** 100 µg
- **Adolescents:** 200 µg
- **Pregnancy and lactation:** 400 µg.

Deficiency

- **Etiology:** Inadequate dietary intake or a disease process, e.g. malabsorption. It may occur in isolated form or in combination with other deficiencies such as vitamin B₁₂, iron, protein and PEM. Deficiency causes impairment of DNA synthesis resulting in defective cell division. Rapidly dividing cells such as in bone marrow and intestinal mucosa are adversely affected.
- **Clinical features:** Megaloblastic anemia, neural tube defects (NTDs) (Fig. 14.5), cleft lip/palate. In adults, it is implicated in Alzheimer disease, dementia, depression, and hearing loss.

Diagnosis

By and large clinical.

Treatment

0.5–1 mg of folic acid daily.

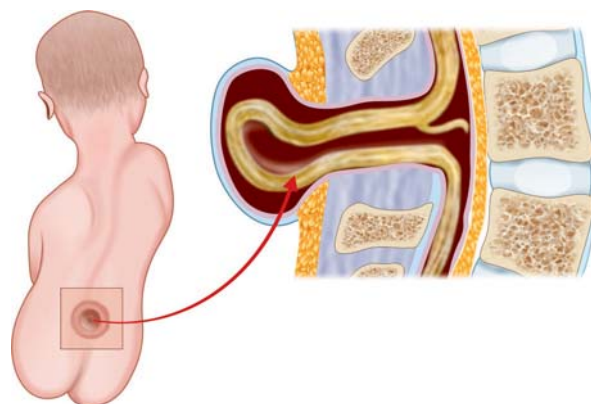


Fig. 14.5: Maternal folic acid deficiency. Note the neural tube defect (meningocele) in the infant born to such a mother. Periconceptional folic acid therapy has now become a universal recommendation.

230 Prevention

For prevention of NTDs, periconceptional folic acid therapy one month before and 2–3 months after conception.

Since folic acid is available as only 5 mg tablets, its one tablet daily is prescribed for periconceptional therapy. No adverse effects are known even with this high dose.

VITAMIN C

(Ascorbic Acid)

This structurally glucose-related vitamin is not synthesized by the body. It is known for its unique property of reversible oxidation-reduction.

- **Functions:** Ascorbic acid which structurally resembles a monosaccharide sugar is known to play important role in oxidation of tyrosine and phenylalanine, information of hydroxyproline, in preventing depolymerization of collagen, maintaining integrity of ground substance, and in hemopoiesis.
- **Dietary sources:** Citrus fruits–Indian goose berry (amla), guava, lemon, orange, grapes, GLVs, soaked cereals.
- **Daily requirement**
 - **Infants and children:** 30–40 mg
 - **Pregnancy and lactation:** 60 mg.

Deficiency

Deficiency of vitamin C, though quite common in its subclinical form, has virtually disappeared in its overt form from the affluent countries. However, frank cases still continue to be seen from time to time in some parts of the developing regions.

Scurvy

Earliest description of scurvy goes back to 1650 when Francis Glisson reported the first case of infantile scurvy.

Etiopathogenesis

Scurvy may occur in the following situations:

- Primary PEM, though during periods of gross retardation of growth, overt scurvy is usually not seen as is the case with rickets.
- Secondary PEM as in malabsorption.
- Exclusively artificially-fed infants.
- Even breastfed infants born to mothers deficient in vitamin C.
- Vitamin C dependency occurring in newborns accustomed to saturation levels of vitamin C since the mother had been taking very high doses of it during pregnancy to prevent colds, etc.
- Infections which enhance the requirement of vitamin C.

The deficiency results in two major changes. **First**, there is impaired collagen synthesis, causing defective formation of osteoid and dentine. **Secondly**, there is a modification of the intercellular ground substance that binds the cells of the capillary walls. All this may lead to changes in the calcified tissues and capillary hemorrhages. In addition, there is an impaired wound healing and susceptibility to infections.

Clinical Features

Scurvy occurs usually in infants between the age of 6 months and 2 years. No age is a bar.

■ **Infantile scurvy** is characterized by:

- Gross irritability, excessive crying and tenderness to touch, more so in the lower limbs. The infant adopts the so-called **frog-position** in which he lies with the lower limbs that are partially flexed at the knees and hips and externally rotated. The posture of the lower limbs gives an impression as though these are paralyzed (pseudoparalysis).
- The palpable subperiosteal hemorrhage into the lower third of the femur may contribute to pain, thus preventing movements of the leg further and strengthening the impression that the limb may be paralyzed.
- Hemorrhages may occur into the skin (Fig. 14.6) and mucous membranes. Perifollicular hyperkeratotic papules, often on the shins appear as reddish/bluish bruise-like spots surrounding hair follicles. The central hairs are twisted like corkscrews that may break easily. The papules may join together to form large areas of spontaneous bruising (petechiae, palpable purpura, ecchymoses).
- Hemorrhages into the gums may result in spongy, swollen, bluish purple gums, especially about the erupted teeth.
- Hemorrhages in the internal organs may cause hematuria, melena, proptosis and subdural swellings. Mild to moderate anemia is usual.
- Scorbutic rosary may result from posterior displacement of the sternum. Unlike rachitic rosary, it is tender, sharp and angular and has a step-shaped configuration, the sternum, being depressed.

■ **Childhood scurvy** presents as:

- Follicular hyperkeratosis with development of minute hemorrhages at the root of the hair follicles.
- Bleeding into the skin, leading to petechiae or even large purpuric swellings, and gums may occur, but subperiosteal hemorrhages are infrequent.



Fig. 14.6: Corkscrew hair in scurvy. Note the bruising around the hair follicle and follicular hyperkeratosis. In vitamin A deficiency (VAD) skin shows follicular hyperkeratosis, but without hemorrhages.

Differential Diagnosis

- Pseudoparalysis of scurvy needs to be differentiated from the true paralysis of poliomyelitis. If the child is held at the shoulders and lifted, he will flex his legs and not allow these to touch the ground because of fear of pain in case of scurvy. In poliomyelitis, the paralysis is truly flaccid. In this situation, the infant's legs will just fall helpless on the ground rather than be lifted as in scurvy.
- Pseudoparalysis may also occur in:
 - Syphilis
 - Suppurative arthritis
 - Osteomyelitis.
 In the former, other signs of the disease are usually present, whereas the latter two conditions are usually unilateral.
- Subperiosteal hemorrhage causing swelling over lower end of femur may have to be differentiated from hemarthrosis of hemophilia.
- Bleeding into skin and mucous membranes needs to be differentiated from the bleeding diathesis of immune/idiopathic thrombocytopenic purpura (ITP) and leukemia.

Diagnosis

Once clinical suspicion is aroused, the diagnosis may be confirmed by the following investigations:

- Ascorbic acid level in serum, white cells or buffy coat, i.e. platelet layer, is usually less than 0.1 mg%.
- Excretion of ascorbic acid in urine below 1.5 mg after a loading dose of 20 mg/kg by intravenous route 4 hours earlier.
- No or less than 20% excretion of ascorbic acid in urine after a loading dose of 10 mg/kg by oral route 24 hours earlier.
- **X-ray changes:** Classical changes may be seen especially in the X-ray knee including lower part of femur and upper parts of tibia and fibula (Figs 14.7 and 14.8). A dense irregular white line, called **white line of Fraenkel**, appears at the epiphyseal ends of the long bones. Subsequently, adjacent to this line occurs an area of destruction (rarefaction). This area is called **fracture zone**. This is very susceptible to fractures and fissuring. The projection of the white line laterally, away from the limit of the shaft, may lead to formation of a spur or marginal cleft. This is what is known as **Corner sign**. It has great diagnostic value.

The rarefied epiphyseal centers may be sharply outlined. This is termed **signet-ring** or simply **ringing of the epiphysis**. There may also be epiphyseal separation. The cortex is thinned because of generalized osteoporosis and the trabeculae have ground glass appearance.

Large subperiosteal hemorrhage may lead to lifting of the periosteum (Fig. 14.9). This is seen as a regional increase in the soft tissue density. The affected bone looks like a dumb-bell or a club. Later, when the hematoma is calcified during healing, it may become clearly visible in the X-ray.

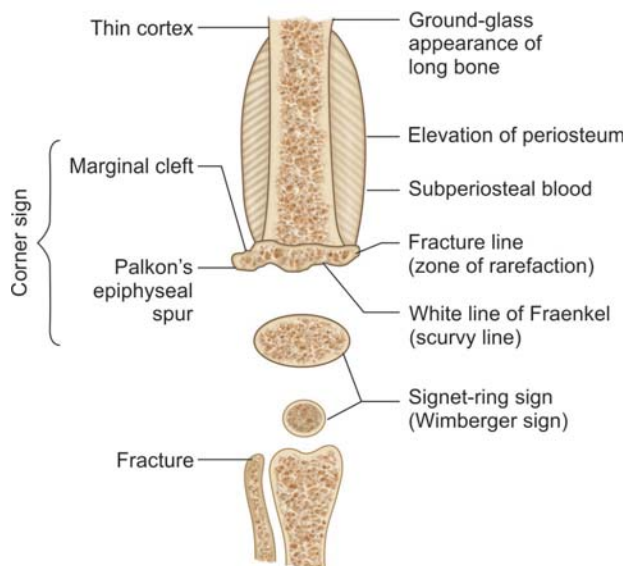


Fig. 14.7: Scurvy. Diagrammatic representation of radiological picture at knee joint and participating long bones.

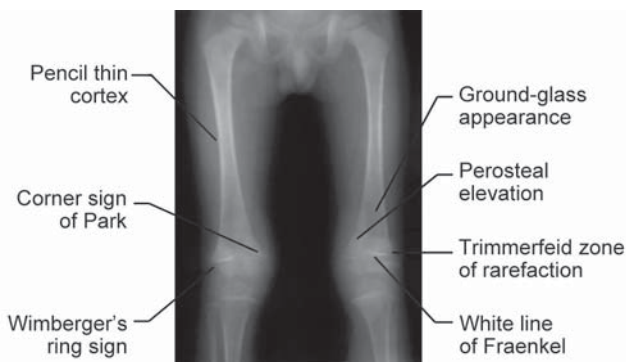


Fig. 14.8: Scurvy. Note the classical radiological signs in X-ray of knee and participating long bones.



Fig. 14.9: Subperiosteal hemorrhage in scurvy.

In Menkes (kinky hair) disease, a sex-linked recessive neurodegenerative disorder due to copper deficiency, radiologic changes simulating scurvy may be observed.

Treatment

It consists in giving a loading dose of 500 mg of vitamin C followed by a daily dose of 100–300 mg for several weeks.

232 Oral administration is good enough. Clinical response occurs rapidly—within 24–48 hours. Improvement in the radiological picture takes a week or two. Subperiosteal hemorrhages are likely to take months to disappear.

Prevention

- Mothers should be encouraged to breastfeed the babies.
- Supplements of vitamin C providing about 25 mg of it daily, should be introduced in the second or third month, especially in infants on artificial feeding.
- Mothers should be advised not to boil fruit juices. Boiling is known to destroy this vitamin.
- Lactating mothers should receive additional vitamin C, their daily need being 100–150 mg of it.
- Intake of amla (Indian gooseberry), guava, tomato, orange, lemon, peas, beans, etc. which constitute rich sources of vitamin C should be encouraged in case of older children and pregnant and lactating mothers.

FAT-SOLUBLE VITAMINS

VITAMIN A

(Retinol)

Vitamin A, a fat-soluble alcohol, is derived primarily from a plant pigment, β -carotene, which plays a vital role in the photochemical basis of vision. Conversion of carotene to vitamin A occurs in the intestinal wall and its absorption into the lymphatic system is facilitated by bile. It is concerned with the maintenance of epithelial tissue in the body, especially that of eye, skin and mucous membrane.

- **Dietary sources:** Shark and cod-liver oil, dark green leafy vegetables (DGLV), e.g. fenugreek, carrot, oranges, tomatoes; fortified infant formulas and foodstuffs.
- **Daily requirement**
 - **Infants:** 300–400 μ g
 - **Children:** 400–600 μ g
 - **Adolescents:** 750 μ g. 1 μ g = 3.3 IU.
- **Functions:** Maintenance of vision, epithelium and differentiation of various tissues in utero.

Deficiency

Deficiency signs of vitamin A deficiency (VAD) may be ocular or extraocular (details vide infra) and also clinical or subclinical depending on the magnitude of deficiency.

Excess/Toxicity (Hypervitaminosis A)

Abuse of vitamin A (more than 20,000 IU daily over several months) may cause toxicity (hypervitaminosis A).

- **Manifestations** include hyperirritability, anorexia, lassitude, headache, alopecia and/or coarsening of scalp hair, desquamation of skin (note in VAD it is hyperkeratosis), fever, benign raised intracranial pressure (ICP) (pseudotumor cerebri), hepatosplenomegaly and tender swellings of the bones.
- **X-ray** shows cortical hyperostosis of long bones (ulna, tibia, etc.), most marked in the middle of the shaft with sparing of the metaphysis.

Even teratogenicity in the form of malformations (often resulting in abortions) may be encountered in infants of mothers who are on retinoic acid for acne or cancer during first trimester of pregnancy. **Gulf syndrome** refers to hypervitaminosis A plus D secondary to excessive consumption of fish oil pearls marketed by Gulf countries.

Vitamin A Deficiency (VAD)

Deficiency of vitamin A, **xerophthalmia**, a leading cause of blindness among the underprivileged continues to be a problem of public health magnitude in the developing world. Of the 10 million children suffering every year from xerophthalmia, 5 million belong to Asia. One-fourth of them are eventually blinded. Half a million go blind in India alone every year.

Etiology

Vitamin A deficiency usually occurs in association with malnutrition and chronic intestinal disorders such as malabsorption states, chronic diarrheal disease, pancreatic disease like cystic fibrosis and hepatic insufficiency. In these situations, vitamin A absorption or metabolism is disturbed.

Diarrhea is a risk factor for VAD; vice versa also is true. Severe measles too is a risk factor for vitamin A deficiency.

Prevalence

The precise incidence of xerophthalmia in the pediatric population defies evaluation. In general, 3–10% of the infants and children in the resource-limited countries suffer from it. Following proactive measures on a large scale, prevalence in India has considerably fallen.

Clinical Features

Ocular Manifestations (Figs 14.10 to 14.17)

The earliest manifestation, **night blindness** or **poor dark adaptation**, is due to insufficient formation of the visual purple (rhodopsin), the rose-red pigment in the rods. Often, the mother of the infant observes that he takes considerable time to adjust to dim light or darkness.

Xerosis of conjunctiva is usually the first sign that can be seen on examination. The conjunctiva becomes dry, lusterless, wrinkled and dirty-brown in color. These changes are most obvious in the interpalpebral bulbar conjunctiva. In advanced cases, significantly evident involvement of conjunctiva over the lower lid and lower fornix may be present (Box 14.2).

Conjunctival xerosis may lead to formation of the so-called **Bitot spot*** which consists of an almost triangular area, usually about the lateral aspect of the limbus, covered by fine, white, foamy or greasy substance. It is basically a heaped-up dry mass of conjunctival epithelium (Fig. 14.14). The appearance is like grains on chalky, pasty foam. Bitot spots are generally seen in both the eyes and are present far more frequently to the lateral than the medial of the limbus.

Keratomalacia is the advanced stage of xerophthalmia. It consists of softening, necrosis and ulceration of

* Bitot spots named after the French physician who described them in 1980s.



Fig. 14.10: Bitot's spot. Note the position of the lesion and its shape. The foamy deposit lies on top of a patch of pigmented conjunctiva.



Fig. 14.13: Xerophthalmia. Bulging staphyloma in a 4-year-old girl.



Fig. 14.11: Xerophthalmia. Xerosis, wrinkling and pigmentation of conjunctiva in a 2-year-old girl. Note the dull cornea and blurred flash reflex.



Fig. 14.14: Xerophthalmia. Bitot's spots and wrinkled, dry conjunctiva in a 3-year-old boy with night-blindness.



Fig. 14.12: Xerophthalmia. Bitot's spot with localized xerosis and pigmentation in a 4-year-old boy.



Fig. 14.15: Xerophthalmia. Bulging staphyloma in a 4-year-old girl.

the cornea. Unlike the preceding stage of corneal xerosis, keratomalacia is irreversible, except for the possible replacement of the grossly damaged cornea by a transplant. Once cornea gets involved, photophobia accompanies the clinical profile.

With the onset of keratomalacia, cornea melts into a dead-white to dirty-yellow structure; invasion by an infection (which is quite usual) further aggravates the situation. If corneal perforation occurs (which again is quite frequent), herniation of the lens and vitreous may result (Fig. 14.17).

Eventually, *panophthalmitis* leads to almost total destruction of not just the cornea, but that of the whole eyeball. Irreversible blindness (which was entirely preventable) is the final outcome, the eye ending up as a shrunken globe.

During the course of destruction of the globe, retina does not lag behind in suffering. On funduscopy, it reveals small white spots and granules, the so-called *fundus ophthalmicus*.



Fig. 14.16: Xerophthalmia. Phthisis bulbi as a result of vitamin A deficiency in a 3-year-old girl who has gone blind.



Fig. 14.17: VAD. Bilateral corneal opacity.

Box 14.2

World Health Organization (WHO) classification of xerophthalmia

- **XN:** Night blindness
- **XIA:** Conjunctival xerosis
- **XIB:** Bitot spot
- **X2:** Corneal xerosis
- **X3A:** Corneal ulceration/keratomalacia <1/3rd corneal surface
- **X3B:** Corneal ulceration/keratomalacia >1/3rd corneal surface
- **XS:** Corneal scar
- **XF:** Xerophthalmic fundi (white retinal lesions).

Extraocular Manifestations

The extraocular manifestations of VAD are listed in Box 14.3.

Diagnosis

- High index of suspicion from the clinical picture is the most important diagnostic measure. Support may be obtained from the dark adaptation test.
- Objective tests based on vital staining of xerotic conjunctiva (Rose Bengal, lissamine, kajal or other mascara) or conjunctival impression cytology (CIC) may supplement clinical diagnosis of xerophthalmia.
- Determination of plasma or liver retinol (vitamin A) level is helpful. The normal values are 50–100 IU in infants and 100–300 IU in grown up children.

Box 14.3

Extraocular manifestations of vitamin A deficiency

- Dry, scaly skin, especially over the outer aspect of the limbs (follicular hyperkeratosis, toad skin or phrynoderma)
- Hypertrophy or even atrophy of tongue
- Increased susceptibility to infections due to squamous metaplasia of respiratory, gastrointestinal, urinary and vaginal tract epithelium as a result of impaired immune response (both specific and non-specific)
- Increased susceptibility to renal and vesical calculi
- Growth failure
- Pseudotumor cerebri
- Infertility
- Fetal defects.

- Vitamin A absorption test may be carried out by giving 0.2 mL/kg of cod liver oil by mouth. Blood samples are obtained before its administration and thereafter at 3, 5, 7, 9 and 12 hours. Afterwards, a curve is plotted from the vitamin A values obtained on these samples. A flat curve indicates defective absorption.

Treatment

The currently recommended World Health Organization (WHO)/United Nation Children Emergency Funds (UNICEF) schedule for treatment of xerophthalmia is summarized in Box 14.4. An oily preparation for oral and a water-miscible preparation for injection is the current recommendation. Steroids may be of help if used early enough in these cases. Almost all cases recover fully without any sequelae.

Prevention

- An intake of at least 1500 IU/day in infants and children less than 4 years and 5000 IU/day in grown up children should be ensured. Just milk meets this requirement in infants. Older children need leafy vegetables and red palm oil in addition to milk.
- According to the National Vitamin A prophylaxis program, all children in the age group 9 months to 3 years in the target areas should receive 100,000 IU for less than 1 year and 200,000 IU for more than 1 year of vitamin A (in an oily base) orally every six months a total of five doses. The agent is supplied as syrup of 100,000 units of vitamin A/mL.
- For preventive purposes, use of β -carotene-rich foods, DGLV, say mustard (sarson), spinach (palak), fenugreek

Box 14.4

WHO/UNICEF treatment schedule of xerophthalmia

Children 1 to 6 years and above

- Immediately on diagnosis 200,000 IU vitamin A(O)
- The following day 200,000 IU vitamin A(O)
- Four weeks later 200,000 IU vitamin A(O)

Children under 1 year and under 8 kg weight at any age

- Half the doses as indicated for children 1–6 years and above 10,000 IU vitamin A(O) for 2 weeks
- for night blindness of bitot spot, with a daily dose of

Note: If there is a persistent vomiting or profuse diarrhea, an intramuscular injection of 100,000 IU of water-miscible vitamin A (but not an oil-based preparation) may be substituted for the first dose.

(methi), amaranth (chaulai), drumstick (sahjan), yellow vegetables (carrot), yellow fruits (mango, orange, papaya) and vitamin A-rich foods, say fish, liver, fresh liver oil, dairy products and edible oils, should be encouraged. **Vision by vegetables** is a good slogan.

- Dark green leafy vegetables are an inexpensive and superb source of β -carotene (precursor of vitamin A). Just 40 g of GLV cooked with 2–3 g of oil provide 1200 μ g of β -carotene which is the recommended daily allowance (RDA) as per WHO. Even in malnourished children, absorption of β -carotene is about 70 percent. Children are able to eat enough GLV from a single traditional meal to meet their vitamin A requirement.
- Fortification of commonly-eaten foods with vitamin A can be an effective prophylactic measure in a population.
- Adequate and timely treatment of PEM, intestinal parasitosis and diarrheal disease, especially with supplementation of the intake with DGLV and edible oil, goes a long way in preventing xerophthalmia.
- The pregnant and lactating mothers should get enough of retinol or carotene in their diets.

VITAMIN D

(Sunshine Vitamin)

Functions

Vitamin D, a secondary steroid, plays an important role in calcium and phosphorus homeostasis. It is a precursor of 1, 25-dihydroxyvitamin D₃, a hormone synthesized and secreted by kidneys under the control of parathormone and tissue phosphate levels.

The ultraviolet rays of the sunlight are responsible for converting the 7-dehydrocholesterol that is normally present under the skin, into vitamin D₃ or cholecalciferol. The latter is further converted to 25-hydroxycholecalciferol and 25-hydroxyergocalciferol in the liver. The last two forms are essential for maintenance of adequate calcium and phosphorus concentration in the extracellular fluid and for the formation of bone matrix. It is now established that 25-hydroxycholecalciferol is then converted to 1, 25-dihydroxycholecalciferol. The latter is specifically helpful in promoting synthesis of **calcium transport protein** in the intestinal wall.

Maintenance of blood level of 25-hydroxyvitamin D more than 20 ng/mL is important for maximum health benefits. In short, vitamin D has both skeletal (calcitropic) as well as extra-skeletal (pleiotrophic) role. Extra-skeletal benefits are reportedly as anti-infective, in respiratory disease, immunological disease and malignancies, etc.

Sources

Sources of vitamin D include sunshine (90%) and diet (10%), fish, fish oils, egg (yolk), milk, infant formulas and supplements such as cereals and margarine (butter-like product made of vegetable oils).

Box 14.5

Causes of vitamin D deficiency

- Decreased synthesis by skin
- Decreased nutritional intake
- Prematurity and VLBW
- Decreased maternal stores
- Formula-fed infants
- Malabsorption
- Chronic liver disease—decreased synthesis
- Chronic renal disease
- Drug-induced—antiepileptics, rifampicin, INH.
- Tumors.

Abbreviations: VLBW, very low birth weight; INH, isoniazid hydrazide.

Daily Requirement

Current recommendation is 400 IU of vitamin D per day for all infants, children and adolescents. This is essential to maintain a vitamin D blood level of 20 ng/mL. With the earlier recommendation of just 200 IU, this level is not maintained.

Deficiency

- **Etiology:** Vitamin D deficiency may result from several conditions (Box 14.5).
- **Clinical features:** Vitamin D deficiency may produce and/or be associated with:
 - **Bone-related:** Rickets and osteoporosis
 - **Extra-skeletal:** Susceptibility to infections, muscle pains and weakness, seizures, asthma, malignancies, type II diabetes, hypertension and obesity, details on vitamin D deficiency rickets are given vide infra in this very chapter.

Excess/Toxicity (Hypervitaminosis D)

It produces clinical manifestation via hypercalcemia due to excessive bone resorption when vitamin D is taken more than 1000 IU/day by infants and 2,000 IU/day by adolescents over several months.

Manifestations include anorexia, excessive irritability, abdominal pain, vomiting, constipation, polyuria, dehydration and hypernatremia, Caffey's disease-like painful cortical thickening of certain bones (mandible, clavicle, ulna, and radius) and ectopic calcification.

Serious adverse effects relate to cardiovascular system (CVS) (hypertension, decreased QT interval, arrhythmias), central nervous system (CNS) (hypotonia, depression, hallucinations, psychosis, coma) and kidneys (chronic renal failure from renal calculi), even pancreatitis may occur.

Gulf syndrome refers to hypervitaminosis D along with A as a result of excessive consumption of fish oil pearls marketed by Gulf countries. Response to withdrawal of vitamin D and calcium and therapy with normal saline, loop diuretics, aluminium hydroxide suffices in most cases.

Prednisolone, calcitonin, chelating agent (sodium versenate), biphosphonates and hemodialysis may be considered in severe hypercalcemia.

236 Vitamin D Deficiency Rickets

(Nutritional Rickets)

Classically, vitamin D deficiency predominantly causes defect of bones, i.e. rickets in growing infants and children before closure of epiphysis. Osteomalacia is characterized by spongy trabecular bones also resulting from demineralization as a consequence of vitamin D deficiency, but after the closure of epiphysis, i.e. in adults.

Certain Terms and Semantics

Before embarking on rickets, it is important to have a clear understanding of certain terms and semantics in relation to bone formation and development of rickets (Box 14.6).

Etiology

Despite such a lot of sunshine, its incidence continues to be high in India and other countries of the third World. This appears to be due to poor dietary intake of vitamin D and also due to poor exposure to sunlight. The latter seems to be related to the widely-prevalent practice of covering the infants with loads of clothes and from living in slums and crowded places. Poor exposure to sunlight may also be related to the inactivity of the malnourished children.

Disturbed metabolism and poor synthesis of vitamin D from the skin, malabsorption state, diarrheal disease and excessive phytate with low calcium and low phosphate content of the diet may well be other causes of rickets in malnourished children.

Our repeated observations of development of rickets in later age-group too, suboptimal intake of calcium and more gratifying response to a combination of vitamin D and calcium than to vitamin D alone in India strongly indicate that both vitamin D and calcium (and perhaps phosphate too) deficiency contribute to the continuing high incidence of nutritional rickets in India and other developing countries.

Box 14.6

Certain terms and semantics

- **Collagen:** The fibrous protein constituent of connective tissues, e.g. bone, cartilage and tendon, etc.
- **Matrix:** It is collagen plus mineralization; normally a healthy bone.
- **Osteoid:** It is the bone protein matrix, composed primarily of type 1 collagen. When there is insufficient mineral or osteoblast dysfunction, the osteoid does not mineralize properly and it accumulates. The unmineralized osteoid has consistency similar to the tip of the nose, instead of the normal hard bone in the bridge of the nose. In children, its focus is on growth plate (no such plate in adults).
- **Rickets:** Lack of mineralization in bone (occurs in infants and children). In it epiphyseal growth plate not closed. Defective mineralization occurs in both bone and cartilage of epiphyseal growth plate.
- **Osteomalacia:** Disorder of mature bones in adult (after epiphyseal growth plate closure) in which mineralization of new osteoid bone is inadequate or delayed.
- **Osteoporosis:** Reduced bone mass, i.e. a bone density of 2.5 SD of a young adult. This is typically measured by dual-energy X-ray absorptiometry at the hip.

Obviously the problem of calcium deficiency (perhaps, in association with phosphate deficiency), in addition to vitamin D deficiency, in etiology of rickets in developing countries needs greater consideration. The preventive as well as therapeutic implications of this observation are vital.

Predisposing factors for early onset of rickets include:

- Prematurity and low birth weight (LBW)
- Maternal vitamin D deficiency, especially osteomalacia.

Prevalence

Conservatively speaking, vitamin D deficiency rickets should be the problem of temperate climate. Paradoxically, however, it has more or less disappeared from the temperate zones, except in migrant dark-skinned population, in bedridden institutionalized children and in areas where milk supply is not fortified with vitamin D. This is ascribed to health education, enrichment of milk with vitamin D, wide use of vitamin D concentrates, and better standard of living and better health and medical care.

The problem of rickets in India is much greater than its extent suggested by the descriptions in various texts. Congenital rickets is a rare entity occurring in neonates of mothers suffering from osteomalacia. However, rickets of premature and very low birth weight (VLBW) infants is frequent.

Clinical Features

Classically, rickets is a disease of rapidly growing period. The peak incidence is encountered in the age group 6 months to 2 years. It is uncommon in infants under 3 months of age, except in premature and/or VLBW infants (rickets of prematurity) and infants of mothers suffering from osteomalacia during pregnancy (congenital rickets). To less extent, rickets may be encountered in toddlers and adolescents as well.

The **earliest manifestations** are quite vague and non-specific. These include profuse sweating over the forehead (more so during sleep) even in wintery months, irritability and restlessness. The earliest sign is craniotabes.

Head

Bossing (frontal and parietal), macrocephaly with flattening of vertex (box head, caput quadratum or hot-cross-bun*), increased size and delayed closure of fontanels (including posterior fontanel), craniotabes (a peculiar softening of occipital and posterior parietal bones which give in like a ping-pong {table-tennis} ball under pressure from thumb); wide open cranial sutures.

Teeth

Delayed dentition.

Thorax

Rachitic rosary (smooth rounded, nontender costochondral beading as in Figs 14.18 and 14.19), **pigeon-chest**

* Hot-cross-bun may also be seen in chronic hemolytic anemia's, chronic iron-deficiency anemia, congenital (cyanotic) heart disease and skeletal dysplasia. At times, no cause may be forthcoming.



Fig. 14.18: Genu valgum.



Fig. 14.19: Genu varum.

deformity (*pectus carinatum*), **Harrison sulcus** or groove (a depression along the insertion of diaphragm into the ribs), flaring of lower ribs. **Violin-shaped** deformed chest is characteristic.

Infrequently, sternum is unusually depressed, the so-called **pectus excavatum** (Fig. 14.20). A concavity at inferior angle of scapula may be detected.

Spine

Scoliosis, kyphosis; infrequently lordosis. Severe deformity of the spine may end up with disproportionate short stature of short trunk type.

Extremities

Widening of wrists, ankles (with **double malleoli***) and other epiphyses due to expansion and cupping of growing ends of bones; **genu valgum** (**knock-knees**)** in older children (Fig. 14.21) or **genu varum** (**bow legs** usually antero-lateral with the level of bend at junction of middle and lower one-thirds) in toddlers (Fig. 14.22); enhanced tendency for green-stick fractures and bending with deformities.

* Above the normal medial malleolus, there is appearance of another prominence from widened epiphysis. This may be seen, but is more often felt on palpation. It is termed **Marfan sign**.

** Intermalleoli distance more than 0 cm.



Fig. 14.20: Funnel-chest deformity (**pectus excavatum**) in a child with advanced rickets. This deformity is most often familial than because of rickets. In rickets, chest deformity is usually pigeon chest (**pectus carinatum**) rather than **pectus excavatum**.



Fig. 14.21: Rachitic rosary.

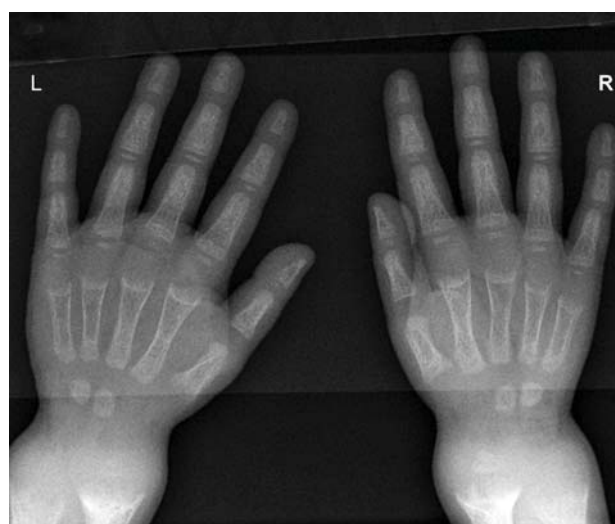


Fig. 14.22: X-ray changes at wrist in rickets.

238 Miscellaneous

- As a result of poor muscle tone (more so in the proximal ones) and relaxation of ligaments, the child may have growth failure, delayed milestones, flat feet, and pot-belly.
- Some degree of **visceroptosis** pushes the liver and spleen downward so that these become palpable without having been enlarged. In such a case scenario, though liver may be considerably palpable below right costal margin, its span remains normal. The upper border comes to lay a space or two below the normal level. At times, laxity of ligaments may be of such a magnitude that the limbs can be bent in to any position. **Acrobatic rickets** is the name given to this condition.
- **Constipation** is often present and is supposed to be secondary to poor muscle tone.
- Rarely, **tetany** may accompany rickets due to reduced level of ionized calcium in plasma. Even seizures may occur in early infancy. Tetany and seizure suggest a defective vitamin D metabolism defect.
- Inadequate mineralization of the collagen renders long bones vulnerable to **fractures** (green stick in infants and toddlers) and **deformities**.
- Dental caries may be seen in some cases of rickets. **Bony tenderness** may be present in some children. If rickets is not adequately treated in time, bone deformities may be left as scar the so-called **old rickets**.
- **Short stature** may also follow. Short stature secondary to rickets is usually disproportionate. Both **short limb** and **short trunk** can occur depending on the predominance of deformities occurring in legs or spine.

Differential Diagnosis

- **Physiological bowing of the legs** seen in some healthy toddlers due to normal deposition of adipose tissue over the lateral aspects is not accompanied by other signs of rickets and disappears in due course of time without any treatment.
- **Physiological knock-knee** as a result of slight valgus position of the feet may also need differentiation from rickets which is likely to have other rickets related signs.
- **Scurvy** manifesting with costochondral beading may cause confusion with similar-looking beading in rickets. Classically, beading in rickets is smooth, rounded and nontender. On the contrary, beading in scurvy is sharp, angular and tender since the problem pertains to collagen rather than mineralization. Some evidence of bleeding is invariably present in scurvy.
- **Child abuse and neglect (CAN)** with fractures may sometime be confused with fractures caused in rickets. A detailed history, physical examination and investigations assist in differentiating the two.
- **Fluorosis** is endemic in some parts of India. In children, it may present with clinical features that resemble rickets. Differentiating features which are characteristic of fluorosis such as dental mottling, osteosclerosis and calcification of ligaments and

known background of high fluoride water levels in water of the area assist in arriving at correct diagnosis.

- **Metaphyseal dysplasia** may present with bow legs, waddling gait, short stature and even rickets-like radiological findings.

Remaining differentials include:

- Renal rickets
- Hepatic rickets
- Malabsorptive rickets
- Drug-induced rickets
- Oncogenous rickets
- Vitamin D-dependent rickets
- Familial hypophosphatemic rickets.

Salient features of these disorders are described later in this very chapter.

Diagnosis**Biochemical**

Biochemical findings include raised alkaline phosphatase (except in malnourished children in whom this may well be normal), usually normal or somewhat low serum calcium and reduced phosphorus.

Today, reduction in the serum 25-hydroxyvitamin D level (<10 µg/mL) is considered a sensitive and reliable index of rickets even in malnourished children. This is the only way to diagnose subclinical vitamin D deficiency.

Radiological

X-ray findings are best seen at the wrist, i.e. lower ends of radius and ulna (Fig. 14.23). These include:

- **Cupping (saucer-like concave depression):** The osteoid (matrix minus mineralization), being radiotranslucent is not seen. In fact the space normally occupied by mineralized matrix is empty.
- **Flaring/splaying (widening):** Everted (out-turned) edges.

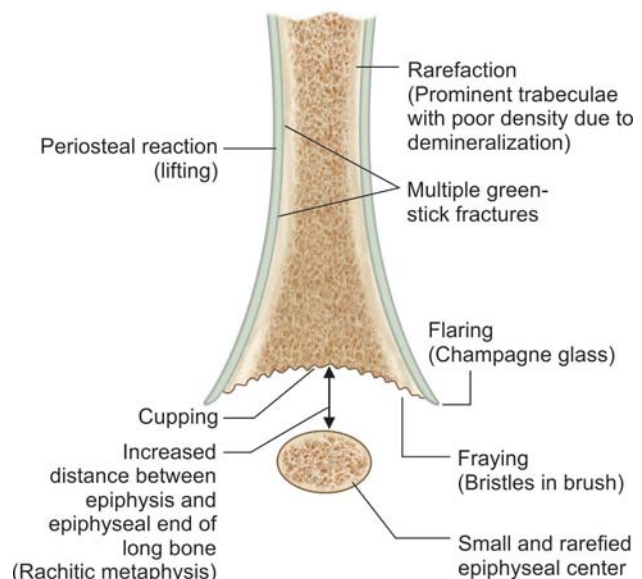


Fig. 14.23: Rickets. Diagrammatic representation of radiologic appearance of radius.

- **Fraying (rarefaction):** Irregular tooth brush-like margin (bottom of the cup).
- Additionally:
 - There is an increase in the distance between the epiphyseal center and metaphysis of long bones due to radiotranslucency of the osteoid.
 - Epiphyseal centers have unclear margins.
 - Periosteal reaction in the form of double shadow of outer contour.
 - Prominence of trabeculae though the shaft shows rarefaction.
 - Green-stick fractures.
 - Bending and deformities.

Overall, long bones have the *champagne glass* appearance.

Treatment

- **Specific treatment:** Stoss therapy consists of administering a single massive dose of vitamin D₃ (3,00,000 units up to 1 year of age; 6,00,000 units for later ages) orally or intramuscularly together with supplementary calcium and phosphorus.

Though serum alkaline phosphatase and phosphorus tend to return to normal within just 5 days, initiation of radiological evidence in the form of appearance of a linear shadow of provisional zone of calcification in 10–14 days with further healing (this zone fusing with the metaphysis as osteoid gets calcified) by 3–4 weeks. Thus, radiologic evidence of healing (say at wrist) is in the form of:

- Appearance of provisional zone of calcification
- Mineralization of **fraying** at the epiphyseal end
- Recalcification of osteoid
- Disappearance of the cupping, fraying and flaring/splaying with adequate mineralization.

In order to achieve real consolidation of cure, it may be desirable to give an additional massive dose of vitamin D after 3–4 weeks. All along, supplements of calcium (100 mg/kg) and phosphorus need to be given. Alternatively, the child may be treated with:

- 60,000 units of vitamin D₃ daily orally for 10 days
- 20,000 units of vitamin D₃ daily orally for 30 days.

- **Surgical intervention:** Gross orthopedic deformities, especially in adolescents, may occasionally need surgical correction (say osteotomy).

Prognosis

As a rule, response to pharmacotherapy is gratifying. However, in an occasional child, a poor response to adequate doses of vitamin D₃ may be encountered. In such a case scenario, probability of refractory or resistant rickets should be considered and the child investigated for the following conditions:

- Malabsorption state, e.g. celiac disease, endemic tropical sprue, cystic fibrosis
- Renal rickets—chronic renal disease and renal tubular acidosis (Fanconi syndrome, Lowe syndrome)
- Prolonged anticonvulsant therapy
- Chronic liver disease etc

- Magnesium deficiency
- Hereditary vitamin D dependent rickets
- Familial hypophosphatemic rickets
- Oncogenous rickets.

Prevention

Availability of at least 400 IU (not 200 as was believed earlier) of vitamin D through sunshine, diet or supplements must be ensured. Now it is a standard practice to supplement all infants in the first year of life with 400 IU of vitamin D. Health education to parents against overclothing the infants and young children and proper housing is important.

Long-term Complications (Sequelae)

Most infants and children with vitamin D deficiency rickets recover fully following timely and adequate therapy. Delayed treatment may fail to prevent sequelae which are:

- Skeletal deformities
- Fractures
- Slipped femoral epiphysis
- Short stature (disproportionate; short trunk or short limb).

Other Types of Rickets

(Rickets other than Vitamin D Deficiency Rickets)

Rickets of Prematurity

(Metabolic Bone Disease of Premature Infants)

Significant mineralization of fetal bones occurs in the last trimester of pregnancy. The premature infant, therefore, considerably loses that opportunity. He stands high chances of developing osteopenia and rickets. Use of frusemide and steroids enhances vulnerability to these problems.

Manifestations include poor growth, frontal bossing, craniotabes, costochondral beading, and epiphyseal widening (most prominent at wrist). Response to vitamin D plus calcium and phosphorus is gratifying with appearance of healing line in the X-ray of wrist in 3–4 weeks.

Malabsorptive Rickets

(Celiac Rickets)

All major malabsorptive states such as celiac disease, tropical sprue and cystic fibrosis may have rickets associated with them because of poor absorption of vitamin D and minerals.

Drug-induced Rickets

Prolonged therapy with antiepileptic drugs (AEDs)/anti-convulsant drugs like phenobarbital, phenytoin, carbamazepine, valproate and lamotrigine increase vitamin D metabolism and enhance vulnerability to development of rickets. The mechanism involved is induction of hepatic cytochrome P-450 enzyme which converts 25(OH)D₃ to inactive (polar) vitamin D₃. Anticancer drug, imatinib, and drugs such as outdated tetracyclines may also contribute to development of rickets.

Hepatic Rickets

Children with chronic liver disease such as neonatal cholestasis (say congenital biliary atresia, neonatal hepatic

240 tis, chronic hepatitis, cirrhosis) are vulnerable to development of rickets in due course due to decreased intestinal absorption of vitamin D and decreased hydroxylation by liver.

Hereditary Vitamin D-dependent Rickets

(Pseudodeficiency Rickets)

It is an autosomal recessive disorder involving deficiency of α -25(OH) $_2$ D $_3$. It is characterized by severe rickets which develop in early infancy (at 3–6 months of age) in spite of adequate vitamin D supplements. It fails to respond to vitamin D therapy upto 4,000 units/day. However, response to long-term massive doses of vitamin D $_3$ or, still better, to oral therapy with α -hydroxyvitamin D $_3$ is gratifying.

- **Type I** has enzyme 25-hydroxyvitamin D $_1$ α -hydroxylase deficiency.
 - **Clinical features**, over and above those of vitamin D deficiency rickets, include hypocalcemic tetany or seizures, anemia, and, at times, respiratory difficulty.
 - **Investigations** show similar findings as in vitamin D deficiency rickets plus very low blood levels of 1,25(OH) $_2$ D $_3$ with normal 25(OH)D $_3$.
 - **Treatment** is with α -calcidiol or calcitriol, 1–2 μ g/day, preferably along with calcium and phosphate supplements. Within 6–8 weeks, radiologic healing occurs.
- **Type II** is characterized by end-organ resistance to 1,25(OH) $_2$ D $_3$ which in spite of high level, becomes redundant in action.
 - **Clinical profile** is characterized by early onset of rickets together with alopecia and ectodermal defects such as milia, epidermal cysts and oligodontia.
 - **Investigations** show low blood calcium, secondary hyperparathyroidism and high 1,25(DH) $_2$ D $_3$.
 - **Treatment** is problematic with poor response to vitamin D analog. Long-term therapy with calcium (oral or IV) may prove beneficial.

Refractory Rickets

(Resistant Rickets)

The term, **refractory rickets**, refers to rickets that is resistant to the usually recommended therapeutic doses of vitamin D.

Rickets complicating renal disease, familial hypophosphatemic rickets, oncogenous rickets and magnesium dependent rickets fall under this broad umbrella. However, some authorities consider vitamin D-dependent rickets, malabsorptive rickets, hepatic rickets and drug-induced rickets too belonging to this category.

Renal Rickets

Rickets may complicate renal disease, e.g:

- **Chronic kidney disease**: Tubulointerstitial disease with glomerular filtration rate (GFR) less than 30–35 mL/min/1.73 m 2 may eventually land up with florid

rickets. Laboratory tests show high blood creatinine, phosphate and parathormone.

Treatment is in the form of:

- Restricting intake of phosphate
- Supplements of calcium and vitamin D analog.
- **In renal osteodystrophy**, kidneys fail to form 1,25(OH) $_2$ D $_3$. It is characterized by bone mineralization deficiency, that is a direct result of the electrolyte and endocrine derangements that accompany chronic kidney disease. Renal osteodystrophy can be further divided into metabolic states associated with either high or low bone turnover.
- **Renal tubular acidosis (RTA)**: An important cause of refractory rickets, RTA is characterized by hyperchloremic metabolic acidosis, often in association with aminoaciduria, reduced blood phosphate level and low molecular weight proteinuria. Blood urea and creatinine levels remain normal.
- **Fanconi syndrome (cystinosis)**: In this condition, cysteine crystals are found throughout the reticulo-endothelial system. Renal tubular defects include glycosuria, aminoaciduria, tubular acidosis, phosphaturia, potassium loss, and, at times, uricosuria and sodium loss. Rickets associated with this condition needs heavy doses of vitamin D (50,000–300,000 units/day) for healing.
- **Lowe syndrome**: This condition presenting very early in life (first few months) is known for severe rickets. Additional features include motor and cognitive retardation, hypotonia, congenital glaucoma (buphthalmos) and other ocular defects and seizures. Death usually occurs in early childhood from progressive kidney injury secondary to glomerulosclerosis.

Familial Hypophosphatemic Rickets

This type of refractory rickets has X-linked dominance with variable penetrance. Rarely, autosomal recessive inheritance may be encountered. Sporadic cases are also seen.

- **Pathophysiology**: The fundamental pathological defect revolves around poor tubular reabsorption of phosphate. Blood phosphate levels are low. Yet, blood levels of 1,25(OH) $_2$ D $_3$, rather than being high, are low.
- **Clinical features**: Manifestations include short stature, bow legs/knock-knee, coxa vara, craniosynostosis and dental abnormalities with abscesses. Notably, hypocalcemic tetany is absent. The patient's mother is usually short statured with genu varum and fasting hypophosphatemia.
- **Specific laboratory findings**: These include very low blood levels of 1,25(OH) $_2$ D $_3$ and high urinary phosphate excretion with low tubular reabsorption of phosphate.
- **Therapy**: It comprises of oral phosphate, 30–50 mg/kg in 5–6 divided doses. The so-called **Joulié's solution** provides 30.4 mg/mL phosphaste. With this dosage, serum phosphate blood level of 3–3.2 mg/dL is achieved. This level is mandatory for optimal outcome. Along with oral phosphate, vitamin D supplements should be provided. A recommended regimen is alphacalcidol, 25–50 ng/kg/day.

Oncogenous Rickets

(Oncogenic Rickets, Tumor-related Rickets)

Tumor-induced rickets is a syndrome characterized by hypophosphatemia, renal phosphate wasting, and decreased serum $1,25(\text{OH})_2\text{D}_3$ levels. The tumors secrete a fibroblast growth factor which is phosphaturic and causes total body phosphate depletion, leading to rickets (osteomalacia in adults).

Usually these tumors are benign and of small size. Their diagnosis and localization is often difficult. Whole body magnetic resonance imaging (MRI) may prove useful for their detection.

Resection of the causative tumor leads to gratifying outcome with reversal of the biochemical, radiological and clinical abnormalities. Neurofibromatosis (von Recklinghausen disease), epidermal nevus syndrome, and linear nevus syndrome are examples of such tumors. Occasionally, mesenchymal malignant tumors, such as osteosarcoma and fibrosarcoma may also cause oncogenous rickets.

Magnesium-dependent Resistant Rickets

Occasionally, rickets associated with hypomagnesemia may occur. In them, response to treatment with massive doses of vitamin D fails. However, they show an excellent response to oral magnesium-chloride supplementation. It has been suggested that serum-magnesium levels should be determined in all cases of rickets in those who are resistant to vitamin D therapy.

Rickets: Broad Canvas

Finally, though vitamin D deficiency is the most common and the most important cause of rickets, it is not the only cause of rickets. A number of other conditions may contribute to or be responsible for similar clinical picture. A broad etiologic classification of rickets as such including resistant/refractory rickets, is given in Table 14.1.

Table 14.2 presents both clinical and investigative clues to diagnosis of resistant/refractory rickets.

Treatment varies with the etiologic diagnosis. Standard treatment for vitamin D deficiency does not work for other rickets where attention to the fundamental defect becomes important, e.g. malabsorption, chronic liver disease, kidney disease, rickets secondary to some tumors, etc.

- In general, vitamin D resistant rickets needs high doses of vitamin D, 2,000 units/day till bony maturation is complete.
- In familial hypophosphatemic rickets, therapy with phosphates in the form of disodium hydrogen phosphate 13.6 g and phosphoric acid 5.9 g/day is required. In place of vitamin D, $1,25(\text{OH})_2$ vitamin D in a dose of 1 μg /day may be employed for better outcome.
- In case of vitamin D dependent rickets, the recommended dose of vitamin D is 10,000–50,000 units/day. Alternatively, $1,25$ dihydroxyvitamin D_3 , 0.5–2.0 μg /day may be employed for vitamin D-dependent rickets (type I).

Table 14.1: Broad etiologic classification of rickets

Type I rickets

- **Vitamin D deficiency:** Poor consumption, malabsorption states, poor exposure to sunlight.
- **Disturbed vitamin D metabolism from liver disease:** Poor formation of $25(\text{OH})$ vitamin D_3 , degradation of vitamin D_3 to $25(\text{OH})\text{D}-26$, 23-lactone (chronic anticonvulsant therapy causing stimulation of microsomal enzyme in liver).
- **Disturbed vitamin D metabolism from renal disease:** Enzyme, 1-hydroxylase, deficiency in tubules interferes with conversion of $25(\text{OH})$ vitamin D to $1,25(\text{OH})_2$ vitamin D_3 . This is termed **vitamin D-dependent rickets (type I)**. Failure of target cells to form $1,25(\text{OH})_2$ vitamin D. This is termed **vitamin D-dependent rickets (type II)**. Failure of kidney to form $1,25(\text{OH})_3$ vitamin D_3 . This is termed **renal dystrophy**.

Type II rickets

- Poor intake or absorption of phosphates.
- **Defective reabsorption of phosphates by the renal tubules:** Fanconi syndrome, familial hypophosphatemic vitamin D refractory rickets, isolated phosphaturia, renal tubular acidosis, rickets, oncogenous tumors (oncogenous rickets) as in von Recklinghausen disease, epidermal nevus syndrome or linear nevus syndrome.

- Rickets accompanying chronic anticonvulsant therapy may be prevented by ensuring adequate dietary intake of calcium and an extra 500–1,000 IU of vitamin D_3 each day.

VITAMIN E

Alpha-tocopherol is the most biologically active among the eight related fat-soluble compounds formed by the tocopherols and their unsaturated derivatives, the tocotrienols.

- **Dietary sources:** The compound, i.e. vitamin E, occurs naturally in foods eaten by humans, such as vegetable oils including soyabean, wheat, germ, sunflower oil, egg yolk and leafy vegetables.
- **Daily requirement:** Its requirement should, therefore, be according to the intake of polyunsaturated fats. It is claimed to be 0.5 mg for every gram of linoleic acid. Generally speaking, 5–15 mg daily should suffice.
- **Functions:** This vitamin is believed to be important in maintaining the stability of biological membranes. Many of its properties are yet unclear, earning it the designation *shady lady of nutrition*.

Deficiency

In man, vitamin E deficiency is fortunately uncommon. When it occurs, the causes include prematurity and malabsorption and cholestatic states.

- **Clinical features:** In the **premature infant**, vitamin E deficiency produces hemolytic anemia 4–6 weeks after birth. Additional problems include edema, skin changes, retinopathy of prematurity (ROP), bronchopulmonary dysplasia and intraventricular hemorrhage. It is worth noting that the deficiency occurs most often in babies who are being fed the milk that is quite rich in linoleic acid. Another factor that may precipitate vitamin E deficiency and hemolytic anemia in the premature infant is

Table 14.2: Clues to diagnosis of refractory rickets

Clue	Diagnosis
Clinical	
Familial	Familial hypophosphatemic vitamin D refracting rickets, 1-hydroxylase deficiency, vitamin D-dependent rickets, renal tubular acidosis (distal)
Manifesting before 6 months of age	Familial conditions like Fanconi syndrome, cystinosis, 1-hydroxylase deficiency
Manifesting after 6 months of age but before 12 months	X-linked dominant vitamin D refractory rickets
Manifesting in early childhood	Renal tubular acidosis
Manifesting in late childhood	Renal osteodystrophy, glycine phosphaturia
Gross muscle weakness	Renal tubular acidosis, glycine phosphaturia
Renal/ureteric colic	Renal stone, renal tubular acidosis
Nausea, vomiting, lethargy	Renal osteodystrophy, renal tubular acidosis, hypophosphatasia
Mental deficiency, buphthalmos	Lowe syndrome
Highly pigmented skin, cystine crystals in cornea on slit lamp examination	Cystinosis
Sutural diastasis, short ribs, cutaneous dimples, hypotonia, failure to thrive	Hypophosphatasia
Laboratory investigations	
Low phosphate with amino aciduria	Vitamin D deficiency secondary to malabsorption, liver disease, chronic anticonvulsant therapy
Low phosphate without amino aciduria, isolated phosphaturia, normal pH	Familial hypophosphatemic vitamin D refractory rickets, oncogenic tumors
Low pH	Renal tubular acidosis
High phosphate	Renal osteodystrophy

the administration of supplementary iron without added vitamin E.

In **children and adolescents**, manifestations include muscular dystrophy (fatty type), growth retardation, impaired reproductive ability, etc.

Treatment

Premature infants fed on formulas rich in linoleic acid and fortified with iron must receive 0.7 IU of vitamin E/100 kcal or 1 IU/g of linoleic acid to avoid occurrence of hemolytic anemia. Generally, it is given 15–25 mg IU/day.

Some authorities recommended administration of vitamin E (IM) once daily for several days after birth in infants who receive excessive concentration of oxygen.

Excess/Toxicity

Neonatal necrotizing enterocolitis.

VITAMIN K

- **Function:** Vitamin K is concerned with synthesis of coagulation factors II, VII, IX and X in the liver.
- **Dietary sources:** GLV, soyabeans and fish are its natural sources. Enough of this vitamin is produced by the intestinal flora.
- **Daily requirement:**
 - **Birth:** 5 µg
 - **Two years:** 10–12 µg
 - **Later:** 12–30 µg
 - Mother's milk provides only 1.5 µg/100 mL of it.

Deficiency

Etiology

Deficiency of vitamin K may occur in the following situations:

- Newborns before adequate colonization of the intestines by bacterial flora have indeed occurred
- Newborns fed on unsupplemented breast milk. Though both cow and human milk have low content of vitamin K, the former supplies four times more vitamin K than the latter
- Infants fed on unsupplemented milk formulas based on soyabean isolates
- Chronic intestinal parasitosis
- Malabsorption states
- Biliary obstruction
- Oral antibiotics.

Clinical Features

These include:

- **Hemorrhagic disease of the newborn (HDN):** This is the most common manifestation of vitamin K deficiency. Generally, bleeding from the GIT, intracerebral hemorrhage or bleeding from the umbilical stump occurs in the first week, usually round about the third day after birth. Therapy consists of blood transfusion and parenteral administration of vitamin K, 2–5 mg.
- **Very-late vitamin K deficiency-related hemorrhagic disease:** This may occur in older neonates, paraneo-

nates and infants. Whereas factors such as persistent/chronic diarrhea, malabsorption, ascariasis, biliary tract obstruction, poor vitamin K intake and broad-spectrum antibiotics could well be the cause or precipitating factor(s) in many cases, there remain some cases without any well-defined etiologic factor.

Prophylaxis

One mg of vitamin K should be given to all newborns intramuscularly soon after birth for prevention of early-onset vitamin K deficiency bleeding (VKDB). This practice has considerably brought down incidence of early-onset

VKDB. Hence, VKDB is now mostly seen after 2 weeks of age (late-onset VKDB).

Treatment

2–5 mg parenterally.

Excess/Toxicity

Excessive administration of vitamin K especially in pre-term and G-6-PD deficient infants, may cause:

- Hemolytic anemia
- Hyperbilirubinemia
- Kernicterus.

Multiple Choice Questions

- Spot the wrong observation:
 - Scorbutic rosary is sharp, angular and nontender
 - Both deficiency and excess of vitamin A may cause pseudotumor cerebri
 - Calcium should always be given in medicinal form in case of dietary deficiency in a child on Stoss therapy with vitamin D
 - Pellagra is now rarely seen
- Nutritional deficiencies causing dry, hyperkeratotic scaly skin include each of the following, except:
 - Vitamin A deficiency
 - Vitamin C deficiency
 - Linoleic acid deficiency
 - Riboflavin deficiency
- Pick up the wrong matching concerning vitamin deficiency and resultant condition:

A. Vitamin B ₆	Seizures
B. Vitamin B ₁₂	Pica
C. Vitamin B ₂	Angular stomatitis
D. Biotin	Alopecia
- Pick up the wrong matching concerning vitamin deficiency and radiological signs:

A. Scurvy	Wimberger sign, white line of Frankel, zone of rarefaction
B. Rickets	Fraying, flaring, cupping
C. Pellagra	Subperiosteal hemorrhage
D. Hypophosphatasia	Sutural diastasis, short ribs
- All of the following observations about vitamin E are correct, except:
 - Vegetable oils including soyabean, wheat, germ, sunflower oil, egg yolk and leafy vegetables are its rich sources
 - Deficiency occurs most often in babies who are being fed the milk that is quite rich in linoleic acid
 - Deficiency signs include hemolytic anemia, retinopathy of prematurity, bronchopulmonary dysplasia and intraventricular hemorrhage
 - Hypervitaminosis E may cause ecchymosis

Answers

1. A 2. D 3. B 4. C 5. D

Clinical Problem-solving

Review 1

A 3-year-old child, on phenytoin over the past 2 years, presents with knock-knee deformity, widening of wrists and double malleolus. His weight is 16 kg and height 95 cm. There is no evidence of knock-knee in the family.

- Could the cause of knock-knee deformity be nutritional rickets. Though the weight and height are on higher side rather than indicative of undernutrition?
- If the answer is in affirmative, what could have contributed to development of rickets in the absence of undernutrition?
- What should be therapy in such a situation?

contd...

Review 2

An 8-month-old infant suffering from moderate anemia of microcytic hypochromic type showed poor response iron. Investigations ruled out possibility of thalassemia, lead toxicity and chronic infections. Eventually, he showed excellent response to a vitamin.

1. What is the diagnosis?
2. What is the characteristic microscopic picture of bone marrow in this condition?
3. What is its therapy?
4. Can this vitamin be equally effective in a neurological problem not responding to well-known therapies?

Answers**Review 1**

1. Yes, it could well be rickets despite the fact that the toddler is somewhat overweight.
2. This child has been on phenytoin over the preceding 2 years. Chronic phenytoin therapy is known to cause hypophosphatemia, hypocalcemia, and low vitamin D levels which can end up in rickets.
3. Start therapy with vitamin D, 600,000 units (IM or O). A repeat dose may be needed after about 3–4 weeks. Alternatively, oral vitamin D may be given in the form of 60,000 units daily for 10 days. Additionally, supplements of calcium should also be given.

Review 2

1. Pyridoxine-dependency anemia which is an X-linked recessive trait.
2. Bone marrow shows erythroid hyperplasia with nucleated normoblasts containing inclusions, the so-called “sideroblasts” in abundance.
3. Regular administration of pyridoxine. Additionally, phlebotomy may be of added help in older children.
4. Pyridoxine dependency seizures, especially in the neonates.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS/INTERNET

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CERTAIN DEFINITIONS**Micronutrients**

The term, ***micronutrients***, denotes substances which are needed by the body in minute quantities, i.e. μg or mg/day rather than g/day in case of macronutrients to perform various physiological functions. Less than 0.01% of human body is formed by them. Micronutrients include vitamins.

The best known micronutrients are vitamin A, iron and iodine which already have prophylaxis programs at national and international levels.

Trace Elements

The term, ***trace elements (microminerals)***, is by and large synonymous with micronutrients.

Minerals

Minerals are naturally occurring, homogeneous, inorganic substances required by humans in amounts of 100 mg/day or more.

- **Minor minerals** are iron, zinc, copper, chromium, cobalt, iodine, fluorine, manganese and selenium, etc.
- **Major minerals** include sodium, potassium, calcium, phosphorous and magnesium.

Vitamins do not fall under the umbrella of minerals. Of course, these are micronutrients.

CLASSIFICATION

The human body minerals and micronutrients may be categorized as follows:

- **Those known to be essential:**
 - Electrolytes, e.g. sodium and potassium
 - With structural role, e.g. calcium and phosphorus
 - As component of hemoglobin, e.g. iron
 - Minor minerals, e.g. copper, zinc, cobalt and iodine.
- **Those whose precise functions are not yet clear:** For example nickel, tin, silicon, and vanadium.

MICRONUTRIENTS

(Trace Elements, Minor Minerals)

IRON

Human body contains just 3–4 g iron; 75% in hemoglobin, 20% in stores and 5% in myoglobin. Storage as ferritin and hemosiderin is in bone marrow, liver and spleen.

- **Functions:** Hemoglobin formation, normal growth and maintenance of normal immune function. Iron-protein complex in muscle comes in handy in time of need.
Cellular iron is involved in respiratory chains of mitochondria for cellular metabolism. It is critical in brain development.
- **Dietary sources:** Green leafy vegetables (amaranth richest around 30 g/100 g)*, pulses, beans, dried fruits, nuts, cereals, molasses; meat, egg yolk and fish. Milk is a poor source of iron, providing just 0.2 mg/dL .
- **Daily requirements (10–20 mg/day):** Preterm and low birth weight (LBW) infants require $1.5\text{--}2 \text{ mg/kg}$ for the whole first year.

Deficiency

Iron deficiency, a major nutritional problem, exists in two forms:

1. Iron deficiency anemia (IDA) with overt manifestations such as pallor (Fig. 15.1), poor growth and development, reduced learning capacity, cognitive function and work capacity.
2. Iron-deficient stores which sooner or later end up as IDA.



Fig. 15.1: Iron-deficiency anemia. Note severe pallor of palpebral conjunctiva. Over and above protein-energy malnutrition, the child had multiple vitamin deficiency signs and heart failure.

* Spinach, believed to be very rich in iron, provides only 1.14 mg iron against amaranth 22.9%, mustard leaves 16.3% and mint 15.6%.

246 Preterm and LBW infants are at high risk of developing iron deficiency since iron requirement is enhanced on account of rapid postnatal growth.

Excess

Accidental ingestion in excess may cause severe stomatitis and gastritis. Excess supplementation predisposes to risk of infection and hinder absorption and metabolism of other micronutrients.

Chronic overload occurs in thalassemia major with multiple blood transfusions, leading to iron deposits in viscera, especially liver, pancreas, heart, skin and pituitary gland, the so-called **hemosiderosis** and **hemochromatosis**. Iron chelating agents (e.g. desferrioxamine) may be used in such situations.

For more details about IDA, See Chapter 32 (Pediatric Hematology).

IODINE

Iodine is essential for production of thyroid hormones, i.e. triiodothyroxine (T_3) and thyroxine (T_4).

■ Functions:

- Synthesis of thyroid hormones which eventually influence the physical and mental growth and development.
- Regulation of metabolism of nutrients of the body.
- Regulation of functioning of nerves and muscles.

■ Sources: Water, iodized salt, seafoods, fresh-water and fish.

■ Daily requirement: 90–150 mg/day depending on age.

- Less than 6 year: 90 mg,
- 6–12 years: 120 mg,
- 12 years: 150 mg.

Requirement in pregnant and lactating mothers is enhanced, i.e. 200–250 mg daily. Most of the requirement is met from drinking water.

Deficiency

- **Etiology:** Iodine deficient drinking water
- **Clinical features:** It manifests as iodine deficiency disorder (Box 15.1).

Excess

Goiter, iodism (ptyalism, coryza, frontal headache, emaciation, and skin eruptions).

ZINC

Next to iron, zinc is the most abundant trace element in the human body. Its concentration in hair is deemed to reflect the zinc status of a subject. It is also present in erythrocytes, prostate, eye, bone and endocrine glands. Total body zinc content of a newborn is about 60 mg and that of an adult about 1,600 mg.

- **Functions:** It is an essential component (cofactor) of at least 20 enzymes, including alkaline phosphatase, carbonic anhydrase and pancreatic carboxypeptidase required for growth and immunity. It plays a vital role in protein synthesis and ribonucleic acid (RNA).

Box 15.1 Iodine deficiency disorder (IDD)

Etiology

Enlargement of the thyroid gland (Table 15.1). as a result of iodine deficiency. It is endemic in sub-Himalayan belt extending from Ladakh through Himachal Pradesh, Uttar Pradesh, Bihar, Bengal, Sikkim, Bhutan, Assam, Arunachal Pradesh, Meghalaya and Nagaland to Burma. Isolated pockets are being increasingly identified, e.g. Rajasthan, Gujarat, Maharashtra, Madhya Pradesh, Andhra and Kerala. Since sea-water is a rich source of iodine, goiter is rare in population living along the sea coast.

Clinical features

Subclinical deficiency of iodine may manifest in the form of goiter only at puberty or confining to the periods of stress. The public health importance of goiter lies in the high incidence of deafmutism, mental retardation (often accompanying frank cretinism), ataxia and spasticity in the endemic areas.

- **Intrauterine life:** Abortion, stillbirth, congenital defects, perinatal mortality; congenital hypothyroidism (cretinism).
- **Newborn:** Mental retardation, goiter and neonatal hypothyroidism.
- **Infants, children and adolescents:** Goiter, growth retardation, poor cognition and subclinical hypothyroidism.

Prevention

As per India's national goiter control program (in operation since 1962), availability of iodized salt (common salt fortified with sodium or potassium iodate in a ratio of 1 in 40,000) is the most economic, convenient and effective means of mass prophylaxis in endemic areas. An alternative to iodized salt is iodized oil capsules at 6–10 months interval, iodized oil given as an intramuscular injection once in three years, Lugol's iodine periodically and iodization of water supply. Double fortified salts iodine plus iron are also available.

Table 15.1: Clinical grading of thyroid (revised)

Clinical grading	Characteristics
Grade 0a	Thyroid not palpable or if palpable, not larger than normal
Grade 0b	Thyroid distinctly palpable, but usually not visible with the head in a normal or raised position and considered to be definitely larger than normal, i.e. at least as large as the distal phalanx of the subject's thumb
Grade I	Thyroid easily palpable with the head in either a normal or raised position. The presence of a discrete node qualifies a patient for inclusion in this grade
Grade II	Thyroid easily visible at a distance
Grade III	Goiter visible at a distance
Grade IV	Monstrous goiter.

- **Dietary sources:** Meat, liver, fish nuts, grains, dry beans and legumes.
- **Daily requirement (5–15 mg/day):** 1–2 mg/kg in pre-term infants.

Deficiency

- **Etiology:** Zinc deficiency may occur in protein energy malnutrition (PEM), malabsorption states, regional ileitis, rheumatoid arthritis, sickle-cell anemia, achondroplasia, chronic blood loss, excessive sweating and hyperzincuria in catabolic states or viral hepatitis. Prolonged parenteral nutrition, if not supplemented with zinc, may also cause zinc deficiency state. Consump-



Fig. 15.2: Acrodermatitis enteropathica. Note skin lesions and alopecia in an infant with protracted diarrhea, similar skin lesion over perianal area, photophobia, atrophied nails, and failure to thrive. Response to therapy with zinc was gratifying.

tion of fibres and phylates in excess hampers zinc absorption.

- **Clinical features:** Clinical manifestation of zinc deficiency include (Fig. 15.2):
 - **Growth retardation, hypogonadism, anemia and hepatosplenomegaly:** This peculiar syndrome called **adolescent nutritional dwarfing** has been described particularly from Iran and Egypt, though cases have been seen in India and other developing countries. However, a convincing cause and effect relationship between this syndrome and zinc deficiency remains to be established. Also, it has been said that zinc deficiency in such cases may well be due to poor absorption because of phylates, calcium and other dietary components rather than low dietary intake.
 - **Gastrointestinal manifestations:** Protracted diarrhea, delayed wound healing, anorexia, failure to thrive, pica, impaired taste perception (hypogeusia).
 - **Dermatological manifestations:** Hyperkeratotic skin.
 - **Acrodermatitis enteropathica** is an autosomal recessive inborn error of zinc metabolism in which there are skin lesions (dry and scaly, eczematous or vesicobulbous) at the extremities and around the orifices (perioral, perianal), protracted diarrhea, alopecia, atrophy of nails, eye changes (conjunctivitis, blepharitis, photophobia), irritability, stomatitis and failure to thrive. It usually manifests shortly after weaning and shows dramatic and sustained response to therapy with zinc.
 - **Infantile tremor syndrome (ITS)** characterized by tremors (in wakeful hours), anemia, regression of milestones, and mental retardation is also believed to be related to zinc deficiency.

Diagnosis

Diagnosis is usually clinical (prolonged low intake, clinical features, malabsorption and total parenteral nutrition {TPN}). The laboratory confirmation for zinc deficiency may be obtained from a plasma zinc level of below 70 µg/dL or a hair zinc level of below 70 µg/g dry weight.

Treatment

It consists of giving zinc sulfate, 0.2–1 mg of elemental or 1–5 mg of the salt as such per kg body weight per day orally (O). In very severe deficiency states, as high a dose as 20–40 mg/day of elemental zinc may be administered.

Now, 10 mg daily in infants less than six months and 20 mg more than six months in all infants and children with diarrhea is an accepted strategy.

Prophylaxis

Zinc fertilizer strategy is a promising approach to enhance crop volume as well as address zinc deficiency in human.

Excess

Zinc in some excess is fairly safe, except that gastrointestinal upset and copper deficiency may occur. Large accidental ingestion may cause acute kidney injury and copper deficiency syndrome.

COPPER

Copper, rightly called the **iron twin**, plays a vital role in the utilization of iron stores and in the activity of many important enzymes, including cytochrome oxidase, monoamine oxidase, dopamine beta-hydroxylase, delta-aminolevulinic acid dehydrogenase, ascorbic acid dehydrogenase, uricase and tyrosinase.

Total body copper content of a newborn is about 14 mg and that of a young adult about 100 mg. Thus, there is an average growth requirement of 10 µg/day. It is distributed in all tissues of body, including kidney, liver, brain, heart, bone marrow and bones.

Whereas in a newborn as much as 50% of body copper is found in the liver, the corresponding figure in a young adult is only 5%. Thus, just, as is the case with iron, copper stores of an infant are sufficient for the first six months of life. In the liver, copper is incorporated into a protein complex, **ceruloplasmin**.

- **Functions:** Utilization of iron stores and activity of several enzymes.
- **Dietary sources:** Copper is widely distributed in foodstuffs (especially seafood, meat, liver, nuts, seeds) with the exception of milk; breast milk contains 40 µg/dL (levels are high in early milk and gradually decline with lactation) and cow milk 20 µg/dL of it.
- **Daily requirement:** 1–2 mg. In preterm infants 30 µg is enough for maintain normal growth though some authorities recommend a higher intake (120/150 µg).

Deficiency

- **Etiology:** Deficiency may be encountered in the following situations:

- PEM including nutritional rehabilitation employing predominantly soy milk and zinc supplementation in excess
- Malabsorption states
- Chronic diarrheal disease
- Prolonged parenteral feeding without copper supplements
- Premature infants being fed low-copper milk preparations. The maximum risk of copper deficiency in breastfed preterm infants is between age five week and eight months when copper levels in milk decline compared to the early milk.
- **Clinical features:** Failure to thrive (FTT), anemia (microcytic-hypochromic that is refractory to iron therapy), neutropenia, vascular abnormalities, hypopigmental hair and skin, seborrhea-like lesions; osteoporosis, metaphyseal fraying and fractures. Deficient immune function may occur.

Excess

Usually genetic in origin, is associated with Wilson disease, Menke's kinky hair disease, and Indian childhood cirrhosis (ICC) now a rare entity.

COBALT

It is a part of vitamin B12 and is required for iodine utilization. It increases iron absorption.

- **Function:** Iodine utilization and iron absorption
- **Deficiency:** Anemia and goiter.

Excess

Dilated cardiomyopathy (which is indistinguishable from primary dilated cardiomyopathy) and goitre.

SELENIUM

Selenium, an integral part of enzymes, glutathione peroxidase is linked to vitamin E. Being an important antioxidant, it protects cells and membrane against oxidative damage. Selenium and vitamin C both antioxidants are known to spare each other.

Since it is found in the soil, overcultivation leads to depletion of selenium content in the crops.

- **Function:** As an antioxidant, it is cardioprotective as well as liver protective.
- **Dietary sources:** Meat, chicken, fish, egg, seafood; cheese, milk; cashew nuts, Brazil nuts; grains, whole wheat bread; sunflower seeds, garlic and onion. Vegetables and fruits are poor in selenium.
- **Daily requirement:**
 - **Children:** 20–30 µg
 - **Adolescents:** 50–55 µg
 - **Pregnancy and lactation:** 60–70 µg.

Deficiency

- **Etiology:** Malnutrition, TPN, low soil content
- **Clinical Features:** Growth retardation, myalgia, myopathy, cardiomyopathy and liver necrosis, selenium-related dilated cardiomyopathy (Endemic dilated cardiomyopathy {DCM}/Keshan disease) used to be common in certain geographical parts of China. It was

first described in 1979 and may occur in young children and women. It is a preventable cardiomyopathy, but once DCM sets in, total reversal to normality is not possible even with selenium supplementation. Four forms of Keshan's disease are recognized—an acute variety with shock, a subacute variety with both hypotension and congestive heart failure (CHF), a chronic variety with CHF and the fourth one, which presents as asymptomatic cardiomegaly. It is virtually indistinguishable from various presentations of primary DCM.

Excess

Dental caries, alopecia and garlic odor in breath.

CHROMIUM

This micronutrient has an important role in glucose tolerance and in facilitating insulin action.

- **Dietary sources:** Vegetables, fruits, nuts, cereals, pulses, yeast and liver
- **Daily requirement:** 10–70 mg/day.

Deficiency

- **Etiology:** Malnutrition and TPN
- **Clinical features:** Hyperglycemia, glycosuria, peripheral neuritis; poor glucose tolerance complicating malnutrition and total parenteral nutrition (TPN), and neuropathy. It facilitates insulin action.

Excess

Dermatitis and renal failure.

MANGANESE

Manganese is an enzyme cofactor in superoxide dismutase, oxidative phosphorylation and bone mineralization.

- **Daily requirement:** 1–5 mg
- **Dietary sources:** Nuts, vegetables, pulses and cereals.

Deficiency

Growth retardation, weight loss, red hair, hypocholesterolemia, increased prothrombin time. Deficiency usually is associated with PEM and TPN.

Excess

Cholestasis, encephalopathy, basal ganglia disorder, goiter and cardiomyopathy.

FLUORINE

Fluorine is mainly a component of bone and teeth wherein it is found as calcium salt. Only up to 1 ppm in drinking water is desirable; more than 2 ppm in water may cause fluorosis.

- **Function:**
 - Protection of dental enamel and inhibition of dental caries
 - Calcification of bones
 - Antibacterial against *Streptococcus mutans*, known for causing dental decay.
- **Dietary source:** Drinking water, seafoods (fish), cheese and tea.

■ **Daily requirement:**

- **Children:** 7–1 mg/day
- **Adolescents:** 2–3 mg/day.

Deficiency

Dental caries manifesting as loss of luster of enamel, yellow brownish staining and even pitting.

Excess

Fluorosis, both dental (chalky white mottled with brownish staining) and skeletal (fluorine deposits in vertebral column, spine, pelvis, lower limbs; eventually neurologic signs and symptoms, deformities and crippling develop).

MOLYBDENUM

Molybdenum, a component of xanthine oxidase is considered the last trace element.

- **Function:** Important in uric acid metabolism and in preventing dental decay.
- **Dietary sources:** Meat, green leafy vegetables (GLVs), dried beans, dried peas, pulses and whole grain cereals.
- **Daily requirement:** 100–500 µg/day.

Deficiency

- **Etiology:** TPN, poor content
- **Clinical features:** Tachycardia, irritability, central scotoma and upper gastrointestinal tract (mouth and esophagus) malignancies.

Excess

It may unmask gout and cause bony defects like genu valgum (knock-knee deformity).

NICKEL

Nickel is a component of urease and nickel plasmin.

- **Dietary source:** Chocolates, fish and oatmeal.

Deficiency

- **Etiology:** Vitamin B₆ deficiency, kidney disease and liver disease.
- **Signs:** Range from urinary tract infections to severe allergic reactions, most often seen in the form of skin rashes. In very severe cases, paralysis alongside inflammation of the liver and lungs may occur.

Excess

Dermatitis, liver necrosis and lung cancer.

VANADIUM

- **Functions:** Regulation of sodium and metabolism of glucose and lipids (insulin-like role).
- **Dietary sources:** Protein-rich foods (seafoods) and vegetables
- **Deficiency:**
 - **Etiology:** Malnutrition and PEM
 - **Sign:** Nutritional edema
- **Excess:** Manic depression.

SILICON

- **Function:** Silicon is important in cross linkage of collagen.
- **Deficiency:**
 - **Etiology:** TPN.
 - **Signs:** Defective bone growth and growth retardation.
- **Excess:** Fibrosis and granuloma of lung.

ARSENIC

- **Function:** Arsenic is important in hair, skin and nail formation.
- **Source:** Water, foods from soil where arsenic has been used.
- **Deficiency:** Poor hair, skin and nail growth.
- **Excess:** Skin, central nervous system (CNS) and respiratory insult.

MAJOR (MACRO) MINERALS

CALCIUM

This is the most abundant mineral in the human body,

- **Functions:** Almost all (99%) of body calcium is in bones and teeth. The remaining 1% is involved in clotting cascade, nerve conduction, muscle stimulation, vitamin D metabolism and parathyroid function.
- **Metabolism:** Its metabolism is regulated by vitamin D, calcitonin and parathyroid hormone. Normal blood calcium level is 8–11 mg/dL. The ideal blood calcium and phosphorus product should be 40. In order that calcium performs its function well, adequate magnesium, phosphorus and vitamin A, C, D and E should be available in the body.
- **Absorption:** Whereas availability of fat facilitates its absorption from the gut, phytates (cereals) reduce its absorption.
- **Sources:** Milk dairy products and millets (say, ragi) and fruits.
- **Daily requirement:** 500–1000 mg/day. Requirement enhances at prepubertal growth spurt.

Deficiency

- **Etiology:** PEM, strict vegetarian diet, chronic diarrhea, malabsorption syndrome, calcium metabolism abnormalities and LBW.
- **Manifestations:** Tetany, muscle cramps, numbness, tingling, impaired growth, calcium-deficiency rickets, osteoporosis, arthralgia and palpitations.

Toxicity/Excess

Hypercalcemia which may manifest with anorexia, irritability, constipation, nausea, vomiting, soft-tissue swellings and neuropsychiatric symptoms. It may result from vitamin D excess, milk-alkali syndrome, prolonged immobilization, hyperparathyroidism, etc. Idiopathic hypercalcemia (William syndrome) is characterized by elfin facies and supra-aortic stenosis.

250 MAGNESIUM

Next to potassium, it is the most abundant mineral cation in cells; more than 80% being in the bones and skeletal muscles.

- **Functions:** It is involved in:
 - Synthesis of fatty acids, proteins, cyclic adenosine monophosphate (AMP)
 - Oxidative phosphorylation
 - Autonomic control of heart.
- **Sources:** Plant foods (GLVs), bananas, legumes, whole grains/cereals; nuts and meat.
- **Daily requirements:**
 - First six months: 40–50 mg/day
 - Second six months: 60 mg/day
 - Later: 200–300 mg/day
- **Absorption:** GIT with renal tubular reabsorption regulating its balance.

Deficiency

- **Etiology:** These include PEM, diarrheal disease, malabsorption syndrome (MAS), losses through continuous suction or fistulas; chronic renal failure involving renal tubular reabsorption
- **Manifestations:** Irritability, tetany, seizures, increased or decreased reflexes
- **Treatment:**
 - **Mild disease:** Oral magnesium 6 mg (1 tablet); 2–3 times daily
 - **Severe diseased:** Oral magnesium 12 mg (2 tablets); 3–4 times daily
 - **Acute severe hypomagnesemia:** IV infusion of magnesium sulfate (50% solution), 25–50 mg/kg slowly 6 hourly × 2–3 doses. Dose in terms of elemental magnesium is 2.5–5 mg/kg. In renal insufficiency/impairment, dose needs a reduction.

Toxicity/Excess

Toxicity occurs with blood levels more than 5 mg/dL (normal level 1.5–3 mg/dL). Manifestations include respiratory depression, drowsiness and coma. Antidote is calcium which is antagonistic to magnesium.

SODIUM

Human body contains 100 g of this very important constituent of body fluid and cells—50% each in extracellular compartment (ECC) and tissue cells and bones. Normal blood level is around 140 mEq/L. Excretion is in urine and sweat.

- **Functions:** Maintenance of osmotic balance; keeping cells in shape.
- **Dietary sources:** Add up to foods for imparting taste.
- **Daily requirement:** 2–3 mEq/kg/day.

Deficiency

- **Etiology:** Gastroenteritis, diarrhea, cholera, prolonged vomiting, excessive sweating, diuretic therapy, water intoxication, syndrome of inappropriate secretion of antidiuretic hormone (ADH) (SIADH), Addison's disease and chronic kidney injury.
- **Clinical features:** Hyponatremic state.

Excess

Hypernatremia, occurring as a part of dyselectrolytemia in dehydration, prolonged therapy with steroids etc, may manifest as thickened skin (sclerema-like), raised blood pressure, seizures, etc.

Also, See Chapter 16 (Fluids, Electrolytes and Acid-base Balance and Disturbances).

POTASSIUM

This important component of body cell and fluids is mainly (90%) intracellular (in cells of tissues and {Red blood cells} RBCs). Total body content is 250 g. Excretion of surplus potassium is in urine. Normal blood level is 3.5–4.5 mEq/L.

- **Functions:** Assists in growth and development of tissue cells, regulates acid-base balance in cells, and contributes to glycogen synthesis cellular excitability of smooth muscles, skeletal, cardiac and nervous tissue and control of involuntary functions of the muscles.
- **Dietary sources:** Fruits, vegetables, whole bread, grain, dried skimmed milk, fish, meat, legumes and coffee.
- **Daily requirement:** 1–2 mEq/day.

Deficiency

- **Etiology:** Dehydration-associated hypokalemia in prolonged gastroenteritis, diarrhea, vomiting; erratic intravenous (IV) fluid administration (without potassium); digitalis therapy and diabetic ketoacidosis.
- **Clinical features:** Abdominal distention and paralytic ileus.
- **Electrocardiography (ECG):** Flat T waves and U waves.

Excess

Ventricular fibrillation; ECG shows tall tented T waves.

Also, See Chapter 16 (Fluids Electrolytes and Acid-base Balance and Disturbances).

IMPLICATIONS OF MICRONUTRIENTS INTERACTIONS

- **Useful interactions**
 - Vitamin A is known for beneficial effect *via* enhancement of iron absorption.
 - Vitamin C too enhances iron absorption.
- **Adverse interactions**
 - Zinc is known to cause copper deficiency by its depletion.
 - Zinc also competes with iron absorption.
 - High phosphorus interferes with calcium absorption. Infants fed on cow's milk stand fair chances of developing hypocalcemic tetany.

RAINBOW REVOLUTION

This is a term designed to promote through intensified campaign consumption of green, yellow, orange, red (GYOR) vegetables and fruits which are rich sources of micronutrients.

Multiple Choice Questions

- Spot the wrong statement:
 - Minor minerals are iron, zinc, copper, chromium, cobalt, iodine, fluorine, manganese and selenium, etc
 - Major minerals include sodium, potassium, calcium, phosphorous and magnesium
 - Vitamins are neither micronutrients nor minerals
 - The best known micronutrients are vitamin A, iron and iodine
- True observations about iron include all except:
 - Preterm and low birth weight infants require 0.5 mg/kg/day of iron during first year of life
 - Human body contains 3–4 g iron, 50% in hemoglobin, 30% in stores and 20% in myoglobin
 - Green leafy vegetable, amaranth, is a very rich source of iron, providing around 30% iron
 - Excess supplementation predisposes to risk of infection and hinder absorption and metabolism of other micronutrients
- All of the following observations about iodine are true, except:
 - It is essential for production of thyroid hormones, T_3 and T_4
 - Most common manifestation is goiter which is common in coastal areas
 - Goiter is accompanied by high incidence of deaf-mutism, mental retardation (often accompanying frank cretinism), ataxia and spasticity in the endemic areas
 - In infants, children and adolescents, iodine deficiency causes goiter, growth retardation, poor cognition and subclinical hypothyroidism
- Failure to thrive, diarrhea, dermatosis, atrophic nails and hair loss are suggestive of:
 - Zinc deficiency
 - Copper deficiency
 - Linoleic acid deficiency
 - Iron deficiency
- Endemic dilated myopathy is a feature of:
 - Fluorine deficiency
 - Chromium deficiency
 - Selenium deficiency
 - Molybdenum deficiency

Answers

1. C 2. A 3. B 4. A 5. C

Clinical Problem-solving

Review 1

A 4-year-old boy presents with growth retardation, weight loss, red hair, hypocholesterolemia, and increased prothrombin time.

- What is your diagnosis?
- What are the predisposing factors?
- What are dietary sources of the said micronutrient?
- What can be the signs of its excess?

Review 2

A 14-year-old well built girl, who had her menarche about 8 months ago, presents with regression in her academic performance over the past 6 months or so with generalized weakness and lethargy. She is moderately anemic with a hemoglobin of 7.5 g/dL and peripheral blood film showing microcytic hypochromic picture with poikilocytosis and anisocytosis. There is evidence of inattentiveness and poor concentration.

- What is the likely cause of her symptoms and signs?
- Can her academic regression be explained on the basis of your diagnosis?
- What could have precipitated her anemia?

Answers

Review 1

- Manganese deficiency, which is a component of some enzymes and stimulates the development and activity of other enzymes. Manganese superoxide dismutase (MnSOD) is the principal antioxidant in mitochondria. Several enzymes activated by manganese contribute to the metabolism of carbohydrates, amino acids and cholesterol.

contd...

2. Existence of malnutrition and total parenteral nutrition.
3. Nuts, vegetables (especially green leafy), pulses and cereals.
4. Excess of manganese causes basal ganglia disorder cholestasis, encephalopathy, goiter and cardiomyopathy.

Review 2

1. Iron deficiency anemia.
2. Ofcourse, it can be. IDA is known to cause cognitive and behavioral problems, inattentiveness and difficulties in concentration.
3. She had menarche 9 months back. Perhaps, periodic loss of blood precipitated her preexisting mild IDA which led to the varied manifestations, including academic regression.

FURTHER READING

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2. Gupte S. *Pediatric Nutrition*, 2nd edn. New Delhi: Peepee 2012.
3. Gupte S, Gupte SB, Gupte M. *Recent Advances in Pediatrics (Special Vol. 25: Child Nutrition in Practice)*. New Delhi: Jaypee 2016.
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PHYSIOLOGICAL CONSIDERATIONS

TOTAL BODY WATER

Water accounts for 70–80% of a neonate's body weight and 55–60% body weight by the age of 1–2 years.

Total body water (TBW) = $0.61 \times \text{weight (kg)} + 0.251$.

However, TBW is relatively less in obesity since fat is known to have low water content.

TBW consists of two major compartments, **intracellular** and **extracellular**, and the two minor compartments, **transcellular** and **slowly exchangeable compartments** (Fig. 16.1).

- **Intracellular fluid (ICF) volume** represents 30–40% of body weight and is the sum-total of fluids from the cells in different locations.
- **Extracellular fluid (ECF) volume** represents 20–25% of body weight and consists of plasma water and interstitial water. In normal children, ECF constitutes 20–25% of total body weight (TBW). Out of this, 5% is plasma and 15% interstitial water. It is at peak at birth (more than ICF), but drops down postnatally secondary to diuresis. The adult ECF:ICF ratio is reached by one year of age.
ECF = $\text{Weight (kg)} \times 0.239 + 0.325$
- **Transcellular fluid (TCF) volume** represents around 2% of body weight; its most important components being gastrointestinal secretions, urine in kidneys and lower urinary tract, cerebrospinal fluid (CSF) aqueous humor, and synovial, pleural and peritoneal fluids. TCF is affected by transepithelial transport and is accurately described as extracorporeal.
- **Slowly exchangeable fluid (SEF) volume**, representing 8–10% of body weight, is contained in bones, dense connective tissues and cartilages. This fluid is not accessible to the TBW on account of slow exchange

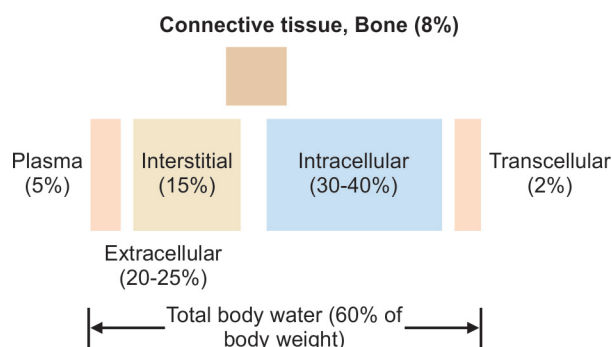


Fig. 16.1: Total body water and its breakup in different compartments as percentage of body weight in a child.

rate. However, the fluid infused into the bone can enter the plasma volume due to the presence of Haversian system, thereby acting as an important factor in situations where intraosseous fluid resuscitation is warranted.

- **Regulation of body water** is controlled by its intake and excretion, the latter being the more vital regulating mechanism. Water intake is normally stimulated by the conscious desire to drink water, i.e. thirst. Thirst, regulated by a centre in the mid-hypothalamus as also by the volume of body water, is interrelated with the antidiuretic hormone (ADH), i.e. arginine vasopressin plus some ADH-independent thirst centers. Increased thirst (polydipsia) or decreased thirst (adipsia) may result from disorders of thirst mechanism as in psychologic/neurologic disorders, malnutrition, potassium deficiency, and defect in renin-angiotensin system.
- **Excretion** refers to obligatory water losses which include insensible losses from lungs and skin, urinary losses, and stool losses. For every 100 kilocalories, fluid losses are 65 mL in urine, 40 mL in sweat, 15 mL in breath, and 5 mL in stools. Urinary water excretion is controlled by two complementary mechanisms:

1. Production, storage and release,
2. Renal epithelial tubular cell response to ADH.

ADH is synthesized in the supraoptic nuclei and is stored in the posterior pituitary. Its release into the blood stream occurs in response to stimuli from the hypothalamus. Effective osmotic pressure of ECF regulates secretion of ADH. The threshold for release of ADH is 280 mOsm/kg of H_2O . As small an alteration in plasma osmolality as 1–2% is capable of initiating or inhibiting its release.

Situations in which ADH secretion is high, inappropriate, or low are listed in Box 16.1. ADH acts primarily by increasing the permeability of the renal collecting ducts to water. Aldosterone, a secretion of the adrenal cortex, enhances tubular reabsorption of sodium, thereby regulating the ECF volume.

ELECTROLYTES

Body water is not just pure H_2O . It contains agents that have the distinction of conducting an electric current in solution. These substances, termed **electrolytes**, may be with positive charge (cations) or negative charge (anions).

- Important cations are sodium, potassium, calcium and magnesium.

Box 16.1**Situation of disturbed antidiuretic hormone (ADH) secretion****High ADH secretion**

- Administration of IV hypertonic saline solution leading to hypertonicity of ECF, fall in plasma or ECF volume,
- Drugs like morphia, phenobarbital, epinephrine, acetylcholine, analgesics and histamine, etc.
- Emotional stress.

Inappropriately high ADH secretion in relation to osmolality of blood

- **CNS disorders:** Meningitis, encephalitis, GBS, tumors, subarachnoid hemorrhage, head injury, perinatal asphyxia, tuberculosis, pneumonias, and certain malignancies.

Low ADH secretion

- Excessive water administration leading to hypotonicity (dilution) of the body fluids.

Abbreviations: ECF, extracellular fluid; CNS, central nervous system; IV, intravenous; GBS, Guillain-Barré syndrome.

- Important anions are chloride, bicarbonate, sulfate, organic acids and protein acids.

Sodium exists predominantly in ECF whereas potassium and phosphates are primarily in ICF. Tonicity of body fluids is termed **osmolality** which means number of osmotically active particles per 1,000 g of water in a solution (mOsm/kg). From clinical point of view, osmolality and osmolarity carry similar meaning. Since sodium and the accompanying anions, chloride and bicarbonate are responsible for 90% of the plasma osmolality, a rough estimate of ECF osmolality can be obtained by doubling the concentration of plasma sodium, except when there is an accompanying hyperglycemia or hyperlipidemia. A more accurate method of obtaining plasma osmolality is by employing the following formula:

$$\text{Plasma osmolality (mg/dL)} = [2 \times (\text{Na} + \text{K})] + (\text{BUN}/2.8) + (\text{glucose}/18)$$

The usual expression employed to denote concentration of electrolytes is mEq/L, 1 mEq being one-hundredth of the equivalent weight which means the weight of the substance in g that is capable of combining or displacing 1 g of hydrogen.

The term, **molality** (also called **molarity**), refers to number of moles in a kg of solvent and a liter of solution, respectively.

The ECF and ICF compartments are normally in osmotic equilibrium except for transient changes. A change in the osmolality of either compartment from the normal (which in case of plasma is 285–295 mOsm/kg) results in rapid movement of water across the highly permeable cell membrane to achieve an equilibration of osmolality. As a rule, water flow from a region of low osmolality to that of high osmolality. Since sodium chloride is the principle osmotic agent in ECF, regulation of body water depends on regulation of sodium.

SODIUM

It is the principal bulk cation responsible for maintenance of ECF volume. Its distribution in body is shown in Table 16.1.

Table 16.1: Distribution of sodium in body

Body components	Percentage of sodium (%)
Exchangeable form	71
Nonexchangeable form	29
Interstitial fluid	29
Plasma fluid	11
Bone	14
Connective tissue	8
Transcellular fluid	2.5
Intracellular fluid (ICF)	2.5

Regulation of Na^+ depends upon:

- **Intake:** It is frequently related to cultural customs. Salt craving is occasionally encountered in patients with salt-wasting syndromes.
- **Absorption:** It occurs through gastrointestinal tract (GIT), except stomach, being maximum in jejunum. Na^+ binds with glucose in presence of binding proteins and is transported into the cell by the Na^+/K^+ activated ATPase system. Aldosterone augments Na^+ absorption.
- **Excretion:** It occurs either through sweat or renal system. Normally, it is 5–10 mEq/L in sweat. In cystic fibrosis and Addison's disease, it is raised. Renal excretion of Na^+ is related to glomerular filtration and tubular reabsorption which, in turn, depend upon renin-angiotensin system and atrial natriuretic peptide.

The kidney is the main organ involved in regulation of water and sodium balance. The main role in regulation of this balance is of ADH, aldosterone and thirst mechanism. In addition, atrial natriuretic peptide is produced by the distention (stretching) of the right atrium in congestive cardiac failure (CCF) leads to loss of water and sodium, thereby cutting down the load on the heart.

POTASSIUM

Potassium (K^+) is the major intracellular cation. As high as 90% is exchangeable. In ICF, K^+ concentration is around 150 mEq/L whereas it is just around 4 mEq/L in ECF.

Its functions include:

- Excitability of nerve and muscle tissue.
- Contractibility of cardiac, skeletal and smooth muscles.
- Maintenance of cell volume (intracellular). It is mainly absorbed from the upper GIT. Both renal and extra-renal mechanisms play role in regulation of potassium balance as follows:
 - Hyperkalemia causes aldosterone production which acts on the distal convoluted tubules, thereby facilitating reabsorption of sodium. This leads to potassium excretion.
 - Aldosterone further leads to potassium loss in saliva, sweat and GIT, thereby contributing to potassium homeostasis.
 - Hyperkalemia stimulates Na^+/K^+ -ATPase pump which leads to non-mineralocorticoid dependent

exchange of sodium and potassium at the level of distal convoluted tubules. Factors promoting potassium movement into the cells include:

- Alkalosis which causes exit of hydrogen ion from the cell and entry of potassium ion into the cell.
- Insulin which enhances potassium uptake by the cell by directly stimulating Na^+/K^+ -ATPase activity.

ACID-BASE BALANCE

An **acid** is a substance that donates a proton (hydrogen ion). A **base**, on the other hand, is a hydrogen ion acceptor.

A **buffer** is a substance that reduces the change in free hydrogen ion concentration of a solution when an acid or base is added.

Aprotics are cations (sodium, potassium, calcium, magnesium) that carry one or more positive charges, or anions (chloride, sulfate) that carry negative charges. They are not capable of either donating or accepting hydrogen ions. Hence, they are not acids, bases or buffers.

It is the concentration of hydrogen ions that determines the acidity of body fluids. If the concentration of hydrogen ion is higher, the fluid is acidic. If the concentration of these ions is less, the fluid is basic or alkaline. In a neutral solution, the number of H and OH ions is equal.

The term **pH** is employed to denote acidity, alkalinity or neutrality. Higher pH means alkalinity and reduced pH acidity. A neutral solution has a pH of 7, blood pH is 7.4 ± 0.05 which means that it is slightly alkaline. Blood pH under 7 and beyond 7.7 is not compatible with life.

Since hydrogen ion concentration is dependent on the ratio of PCO_2 and bicarbonate, pH too is given by this ratio rather than the individual values of the components. If PCO_2 rises by 1 mmHg, pH is lowered by 0.01, if HCO_3^- falls by 1 mEq/L, pH is lowered by 0.02.

Regulation of body pH is by:

- Chemical buffer system in the form of bicarbonate-carbonic acid system (ECF compartment), protein, organic phosphate, hemoglobin (ECF compartment), and phosphate in monohydrogen and dihydrogen forms (urine)
- Pulmonary mechanism which lends support to the bicarbonate-carbonic acid buffer system by eliminating excess CO_2 through rapid breathing. According to Kasires and Bleich equation (which clinically replaces Henderson-Hasselback equation)

$$[\text{H}^+] = 24 + \frac{\text{PCO}_2}{\text{HCO}_3^-}$$

The equation shows that pH depends not on absolute levels of HCO_3^- and PCO_2 but on the ratio of the two concentrations. A decrease or increase in concentration of HCO_3^- does not modify pH if the PCO_2 is lowered or increased in proportion. By altering the rate at which CO_2 is excreted, the lungs can regulate PCO_2 and modify pH.

- Thus, an increased respiratory rate, stimulated by increased CO_2 levels increases CO_2 excretion, resulting in reduced PCO_2 and increased pH.

- Renal mechanism by excreting hydrogen ions as phosphate buffer salts and ammonia ions and by reabsorption of bicarbonates in the proximal tubules.

Under normal conditions, renal mechanism is the most important regulator for acid-base balance. It fulfills two requirements, i.e. preventing loss of HCO_3^- in urine and maintaining plasma HCO_3^- levels by excreting an amount of acid equal to daily production of nonvolatile acids and adding new bicarbonates to blood. This is accomplished by reabsorption of nearly all the filtered HCO_3^- predominantly at the proximal convoluted tubules (80%) and excretion of H^+ ions along with addition of a new HCO_3^- to blood.

Table 16.2 gives the normal values of arterial and venous pH, PCO_2 and HCO_3^- .

Buffer system is the mechanism provided to resist a significant change in the hydrogen ion concentration of the blood when moderate amounts of acid or base are added to it. Box 16.2 lists the various buffers provided in the body.

The following standard equation (Henderson-Hasselbach equation) governs the pH:

$$\text{pH} = \text{pK} (6.1) + \log \frac{\text{Base (Bicarbonate)}}{\text{Acid (Carbonic acid)}}$$

This system enables the body to make up for the various acid-base disturbances and to maintain the blood pH within the normal limits. As for instance, in response to respiratory acidosis, kidney tends to retain bicarbonate, thereby resulting in the so-called **compensatory metabolic alkalosis**. On the other hand, in respiratory alkalosis, the kidney responds by eliminating bicarbonate, resulting in compensatory metabolic acidosis.

Similarly, metabolic acidosis or alkalosis may be followed by compensatory respiratory alkalosis or acidosis through increase or decrease in respiratory rate. Respiratory compensation is more rapid and more powerful than the metabolic compensation.

Table 16.2: Normal levels of blood pH, PCO_2 and HCO_3^-

Criteria	Venous levels	Arterial levels
pH	7.35–7.40	7.38–7.45
PCO_2	45–50 torr	35–45 torr
HCO_3^-	24–25 mEq/L	23–27 mEq/L

Box 16.2

The components of the buffer system provided in the body

- Bicarbonate-carbonic acid buffer; abundant though weak
- Hemoglobin; very powerful
- Proteins
- Bicarbonate-carbonic acid in renal tubules
- Monohydrogen phosphate-dihydrogen phosphate buffer
- Sodium-hydrogen exchange in the distal renal tubules
- Ammonia-ammonium buffer in the distal renal tubules.

256 No doubt compensatory mechanism plays an important role in maintaining the pH of blood. What is equally important is the fact that it never overcorrects the underlying acid-base disturbance.

In order to determine the acid-base status of a child, a gadget, blood gas analyzer, is employed. It measures pH, PCO₂ and Hb concentration. The remaining indices can be calculated from them.

DISORDERS OF FLUID AND ELECTROLYTE BALANCE

DEHYDRATION

Dehydration is a clinical state that results from:

- Loss of body fluids in excess of intake
- Fluid deprivation
- Fall in total quantity of electrolytes.

In order to restore or maintain the normal volume and composition of body fluids, oral or parenteral fluid therapy is mandatory. Such a therapy consists of three phases, namely

1. Deficit replacement
2. Supplemental replacement
3. Maintenance.

The topic is discussed at length in Chapter 29 (Pediatric Gastroenterology).

HYPONATREMIA

It is defined as serum sodium of less than 135 mEq/L.

Etiology

It is caused by conditions that lead to:

- Primary sodium deficit with sodium depletion from renal losses, extrarenal losses or nutritional deficits
- Primary water excess with water gain
- Abnormal retention of sodium and water. For detailed list of causes, see Box 16.3.

Box 16.3 Etiology of hyponatremia

Primary sodium deficit with sodium depletion

- **Renal sodium losses:** Prematurity, renal salt wasting, adrenal insufficiency with mineralocorticoid deficiency, recovery phase of acute tubular necrosis, chronic diuretic therapy, osmotic diuresis in diabetes mellitus, renal tubular acidosis
- **Extrarenal sodium losses:** Vomiting, gastroenteritis/diarrhea, nasogastric drainage, excess sweating, burns, cystic fibrosis.
- **Nutritional deficits:** WIC syndrome, IV fluids poor in sodium, CSF drainage, burns, paracentesis.

Primary water excess with water gain

SIADH, hypothyroidism, excess IV fluids, psychogenic polydipsia, glucocorticoid deficiency, tap-water enema.

Abnormal retention of sodium and water

Nephrotic syndrome, cirrhosis, CCF, renal failure (both acute and chronic).

Abbreviations: WIC, water intoxication; CSF, cerebrospinal fluid; ADH, antidiuretic hormone; SIADH, Syndrome of inappropriate ADH secretion; CCF, congestive cardiac failure.

Clinical Features

Most subjects with serum sodium between 125 and 135 mEq/L are asymptomatic. Depending on the severity of hyponatremia, clinical features include.

Early

- Restlessness, lethargy and confusion
- Headache
- Nausea and vomiting.

Late

- Seizures
- Hypotension
- CCF, arrhythmias, myocardial ischemia
- Central diabetes
- Cerebral edema, raised intracranial pressure (ICP) with papilledema
- Decorticate posturing
- Coma.

Treatment

Symptomatic hyponatremia is treated by administering 3% solution of sodium chloride (saline), 10 mL/kg (maximum 12 mL/kg) at a rate of 1 mL/minute, intravenously. This would correct hyponatremia by approximately 5 mEq/L.

Thereafter, extra sodium needed (calculated as per the formula given below) may be administered slowly spread over 24–48 hours. Rapid correction carries the risk of pontine myelinosis.

$$\text{Sodium deficit (mEq/L)} = \text{serum Na expected (135)} - \text{serum Na (actual)} \times \text{wt (kg)} \times 0.6.$$

In hyponatremia associated with SIADH, water overloading and renal failure, fluid restriction is required to safeguard against pulmonary edema and CCF. In hyponatremia accompanying hypoproteinemia, fluids must not be restricted.

HYPERNATREMIA

It is defined as serum sodium of more than 150 mEq/L.

Etiology

The causes are related to either excessive gain of sodium or excessive loss of water compared to sodium loss (Box 16.4).

Clinical Features

- Tough and doughy skin and subcutaneous tissue
- Irritability, lethargy and confusion
- Twitching, seizures and coma
- Subdural, subarachnoid and intracerebral hemorrhages
- Deep, rapid breathing from associated metabolic acidosis.

Treatment

- If the child is conscious, he is treated with oral rehydration solution (ORS) over and above continuation of breastfeeding and enough of water.
- If the child is in shock, give IV Ringer's lactate or NaCl to correct hypovolemia.

Box 16.4 Etiology of hypernatremia**Excessive sodium gain**

- Erroneously prepared ORS/formula
- Accidental substitution of sodium chloride for glucose in infant formula
- Excessive sodium bicarbonate during resuscitation
- IV administration of hypertonic saline
- Sea-water ingestion
- Hypernatremic enema
- Münchausen by proxy syndrome involving intentional salt poisoning
- High breast milk sodium.

Excessive water loss/deficit

- Diabetes insipidus (both central and nephrogenic)
- Diabetes mellitus
- Age with water loss more than solute loss
- Inadequate breastfeeding
- Poor water intake
- Prematurity accompanied by increased insensible water loss
- Adipsia
- Inadequate excess to free water.

Abbreviation: ORS, oral rehydration salt/solution; IV, intravenous.

- Treat the underlying cause.
- Ensure slow correction of hypernatremia, not more than 0.5 mEq/L/hour or 10 mEq/L/day fall.
- The goal is to bring the serum sodium to 145 mEq/L.
- If serum sodium is over 180 mEq/L, peritoneal dialysis is indicated.
- In case of development of convulsions during treatment (usually because of water intoxication), it is advisable to give 3–5 mL/kg of NaCl or 20% mannitol.
- Correct hypocalcemia.

HYPOKALEMIA

It is defined as a serum potassium level of less than 3.5 mEq/L.

Etiology

Hypokalemia may result from reduced intake, renal losses, extrarenal losses, and fall in muscle mass (Box 16.5).

Clinical Features

- Common manifestations include weakness of skeletal muscles, hypotonia, hyporeflexia, abdominal disten-

Box 16.5 Etiology of hypokalemia**Reduced potassium intake**

Protein energy malnutrition

High renal losses

- **Diuretics:** Osmotic diuretics, carbonic anhydrase inhibitors
- **Tubular defects:** Renal tubular acidosis
- **Acid-base disturbances:** Diabetic ketoacidosis, alkalosis
- **Endocrinopathies:** Cushing syndrome, primary aldosteronism, thyrotoxicosis.

High extrarenal losses

- **Gastrointestinal tract (GIT):** Diarrhea, vomiting, catharsis, frequent enemas, biliary drainage, enterocutaneous fistulas
- **Skin:** Profuse sweating.

Miscellaneous

- Decrease in muscle mass myopathies
- Familial hypokalemic periodic paralysis.

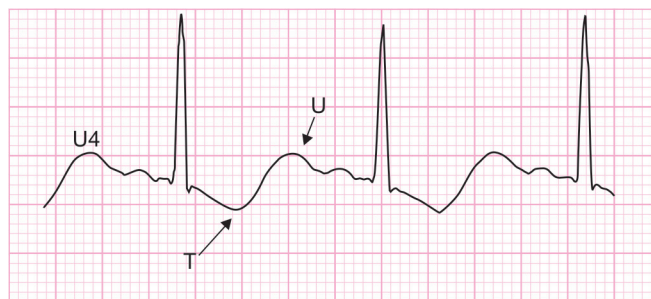


Fig 16.2: Hypokalemia. Note the T wave inversion and prominent U waves.

tion, poor peristalsis, paralytic ileus, frank paralysis and considerable respiratory distress.

- Cardiac involvement may be in the form of arrhythmias and electrocardiograms (ECG) changes which include depression of ST segment, flattening or inversion of T wave, prominent U wave (Fig 16.2) and prolongation of QTc beyond 0.425 sec. Yet severe hypokalemia may further cause prolonged P-R interval, sinoatrial block and extrasystoles (ventricular). Mental apathy may also be encountered.
- Patients on digoxin run the risk of digoxin toxicity in presence of hypokalemia. *Why?* Low potassium level causes binding of digoxin to myocytes so that its clearance gets reduced and its action gets potentiated.
- Prolonged/chronic hypokalemia leads to inability of kidneys to concentrate urine, polyuria, polydipsia and alkalosis. Poor renal function may persist even after correction of hypokalemia.

Diagnosis

- Serum potassium level more than 3.5 mEq/L. A level less than 2.5 points to severe hypokalemia.
- Transtubular potassium gradient (TTKG) test (Box 16.6).

Treatment

- Potassium, 2–3 mEq/kg/ 24 hour, in 3 or 4 doses over 24 hours orally (preferred) or potassium chloride as IV infusate, 0.5–1 mEq/kg with a maximum of 40 mEq over 1 hour (in case of serum potassium less than 2.5 mEq/L or oral intolerance).
The IV fluid must not contain more than 40 mEq/L potassium. Secondly, IV potassium administration should under ECG monitoring.
- Hypokalemia with massive urinary losses should be treated with oral potassium, 10 mEq/kg.

Box 16.6 Transtubular potassium gradients (TTKG) test for renal loss of potassium

$$TTK = \frac{\text{Urine potassium} \times \text{Serum osmolality}}{\text{Serum potassium} \times \text{Urine osmolality}}$$

For this test, it is mandatory that serum osmolality is greater than urine osmolality.

• Interpretation:

- TTKG <4 denotes insignificant renal loss of potassium.
- TTKG >4 denotes significant renal loss

- 258 ■** Indomethacin is indicated in Bartter syndrome (hypokalemia, metabolic alkalosis; clinical features include growth failure, polyuria, polydipsia, recurrent dehydration, muscle weakness, cramps, vomiting, etc).
- MgCl_2 is indicated in Gitelman syndrome (hypokalemia, hypomagnesemia, metabolic acidosis; clinical manifestations less severe than in Bartter syndrome).

HYPERKALEMIA

It is defined as serum potassium of more than 5.5 mEq/L.

Etiology

It usually results from excessive intake (often through IV fluids), impaired excretion (acute/chronic renal failure, adrenal insufficiency, hyporeninemic hypoaldosteronism, potassium-sparing diuretics), shifting or release of potassium from tissues into ECF (acidosis, injury, hemorrhage, burns, hemolysis, insulin deficiency) and drugs (succinylcholine, digitalis toxicity).

Clinical Features

Significant hyperkalemia may cause marked muscular weakness with flaccid paralysis, tetany, paresthesia, bradycardia, shock and cardiac arrhythmias.

ECG changes (Fig. 16.3) include elevation and tenting of T wave, widening of QRS complex, depression of ST segment, prolongation of PR interval and short QT interval.

Treatment

Initial therapy consists in rapid IV administration of sodium bicarbonate, 1–3 mEq/kg, or glucose and insulin (0.5–1 g of 10–20% glucose/kg plus 1 unit crystalline insulin/3 g of glucose) to lower the serum potassium level, and IV calcium gluconate, 0.3–0.5 mL/kg of a 10% solution, slowly to counter the cardiac toxicity. It would be under ECG monitoring.

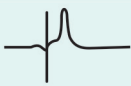


Serum potassium	Typical ECG appearance	Possible ECG abnormalities
Mild (5.5–6.5 meq/L)		<ul style="list-style-type: none"> • Peaked T waves • Prolonged PR segment
Moderate (6.5– 8.0 meq/L)		<ul style="list-style-type: none"> • Loss of P wave • Prolonged QRS complex • ST-segment elevation • Ectopic beats and escape rhythms
Severe (>8.0 meq/L)		<ul style="list-style-type: none"> • Progressive widening of QRS complex • Sine wave • Ventricular fibrillation • Asystole • Axis deviations • Bundle branch blocks • Fascicular blocks

Fig. 16.3: ECG changes in hyperkalemia. Note the changes in mild, moderate and severe hyperkalemia.

*After Adolf Kussmaul, German physician, 1822–1902. Such a labored breathing may occur in renal failure too. The underlying cause is low levels of carbon dioxide associated with hyperventilation. Terminally, bouts of such breathing may be interrupted by spells of apnea, the so-called Cheyne-Stokes breathing.

Eventually, a negative potassium balance is attained by employing ion-exchange resins, e.g. kayexalate, 1 g/kg/24 hr (orally or as retention enema) in 2–4 divided doses, by hemodialysis, or by peritoneal dialysis.

DISTURBANCES OF ACID-BASE BALANCE

METABOLIC ACIDOSIS/ACIDEMIA

Metabolic acidosis means accumulation of acid whereas metabolic acidemia means actual lowering of blood pH because of elevation of hydrogen ion concentration above normal. The former need not necessarily be accompanied by the latter because the accumulation of acid might have been tackled well by the buffer defense mechanism or the compensatory respiratory mechanism.

Etiology

Two categories depending on the elevation or normality of the anion gap (difference between sum-total of cations, sodium and potassium, and sum-total of anions, chloride and bicarbonate; normal up to 16 mEq/L; high is associated with severe illness and greater mortality).

1. Metabolic acidosis associated with an elevated anion gap results from overproduction of endogenous acids (ketoacids in ketoacidosis, or lactic acidosis), underexcretion of fixed acids (advanced renal failure), or ingestion of excess exogenous acids (salicylates, alcohol).
2. Metabolic acidosis associated with a normal anion gap (hyperchloremia) results from net loss of bicarbonate from the kidney (renal tubular acidosis, nephrotoxin-related) or GIT (severe diarrhea).

Clinical Features

- **Mild metabolic acidosis:** Nausea, vomiting, headache and abdominal pain.
- **Significant metabolic acidosis (pH < 7.2):** Respiration becomes deep and rapid (Kussmaul breathing)* and the child becomes drowsy, confused and stuporous. In severe acidosis, peripheral vasodilation, vascular collapse and shock may follow. Often, hyperkalemia may accompany it.
- **Chronic acidosis:** Fatigue and anorexia.

Treatment

- Severe metabolic acidosis (pH < 7.2) is countered by administration of sodium bicarbonate, 1–2 mEq/kg, or, preferably as given by the following formula:

$$\text{Sodium bicarbonate (mEq)} = \text{Bicarbonate deficit (mEq/L)} \times \text{body weight (kg)} \times 0.3$$

Half of the calculated sodium bicarbonate should be given immediately and the remaining half as an infusion in 12–24 hours period. The usually available 7.5% solution providing 0.9 mEq/mL of bicarbonate needs to

be diluted in an equal volume of distilled water (alternatively, double volume of 5% dextrose).

- Management of underlying condition such as diabetes mellitus.
- Simultaneous administration of potassium to safeguard against risk of development of hypokalemia is strongly recommended.
- Calcium gluconate is indicated if the subject develops hypocalcemic tetany following correction of metabolic acidosis.
- In case of severe acidosis with hypernatremia, it is advisable to substitute sodium bicarbonate by trihydroxymethyl-aminomethane (THAM).

METABOLIC ALKALOSIS/ALKALEMIA

Here, plasma pH exceeds 7.45 following net gain of base, net loss of acid or loss of chloride in excess of bicarbonate in fluid.

Etiology

It is caused by:

- Administration of large amounts of alkali, IV or orally (milk alkali syndrome).
- Loss of hydrogen ions (vomiting in hypertrophic pyloric stenosis, prolonged gastric aspiration).
- Acute volume contraction with disproportionate losses of chloride.
- Severe hypokalemia causes metabolic alkalosis by shifting hydrogen ions into the cells.
- Aldosteronism, Bartter syndrome and Cushing syndrome may cause saline-resistant alkalosis, i.e. alkalosis without volume and chloride depletion.

Clinical Features

These include hypoventilation, apathy, confusion, drowsiness, stupor and coma. In addition, alkanotic tetany due to low ionic calcium and cardiac arrhythmias due to hypokalemia may occur.

Treatment

Treatment is indicated only in cases of severe metabolic alkalosis with a pH over 7.5. Most cases respond to administration of saline (isotonic or 1/2 isotonic) infusion with added potassium.

Ammonium chloride or arginine hydrochloride infusion is indicated in cases of severe alkalosis resistant to saline, usually following massive loss of gastric contents. Severe alkalosis in association with renal failure or hyperosmolar state is an indication for hemo- or peritoneal dialysis, or renal replacement therapy.

RESPIRATORY ACIDOSIS/ACIDEMIA

It means marked reduction in blood pH primarily as a result of retention of carbon dioxide or fall in alveolar ventilation. As a result, arterial partial pressure of CO_2 (PaCO_2) goes beyond normal of 44 mmHg and blood pH goes down; <7.35 .

In this situation, kidneys attempt to compensate for respiratory acidosis. It attains this by enhancing reabsorption of

HCO_3^- , beginning next 3–6 hours and concluding by 3–5 days. Kidneys also enhance excretion of ammonia and other hydrogen ions. This results in plasma bicarbonate concentration.

Etiology

Acute respiratory acidosis may follow airway obstruction (bronchial asthma, foreign body, laryngeal edema, croup, and aspiration), lung diseases (respiratory distress syndrome in the newborn, pneumonias, pneumothorax, pulmonary edema, and pulmonary embolism), neuromuscular diseases (Guillain-Barré syndrome, poliomyelitis), brainstem lesions with central depression, oversedation (opium) and child abuse.

Chronic respiratory acidosis may be associated with chronic lung disease like asthma, cystic fibrosis, bronchiectasis, interstitial fibrosis, kyphoscoliosis, Werdnig-Hoffmann disease, etc.

Clinical Features

- Air-hunger with use of accessory muscles (chest retractions).
- Neurological findings—anxiety, lethargy, tremors, confusion, disorientation, somnolence and coma.
- Cardiovascular findings—tachycardia, bounding arterial pulses, hypotension.

Treatment

It consists in treating the underlying etiologic factor(s) and improving alveolar gas exchange by assisted ventilation rather than by IV sodium bicarbonate which may prove counterproductive by causing hyperosmolality and heart failure.

RESPIRATORY ALKALOSIS/ALKALEMIA

It denotes reduction in PCO_2 from hyperventilation or hyperpyrexia, sepsis, central nervous system (CNS) disorder, etc.

Etiology

It results from salicylate intoxication, hyperventilation (hysterical, assisted ventilation on a respirator), hyperpyrexia, CNS disorders (severe hypoxia, stroke, trauma, infection, tumors), heart failure, hepatic encephalopathy, sepsis and drugs (catecholamines, methylxanthines, doxapram, progesterone, nicotine and salicylates).

Clinical Features

Over and above signs and symptoms of the underlying disease, manifestations include numbness, tingling, paresthesia, light headedness, palpitations and in severe cases, tetany and seizures. At times, unconsciousness may result from vasospasm of cerebral vessels because of hypercapnia.

Treatment

It is aimed at correcting the underlying cause. The child nearly always manifests signs and symptoms of the underlying disease. Acidifying agents (ammonium chloride) are not indicated.

260 MIXED ACID-BASE DISTURBANCES

The following four types of mixed acid-base disturbances may also be encountered:

1. **Respiratory acidosis**—metabolic acidosis (e.g. respiratory distress syndrome)
2. **Respiratory acidosis**—metabolic alkalosis (e.g. following use of excessive diuretic therapy in chronic respiratory acidosis in subjects with heart failure)
3. **Metabolic acidosis**—respiratory acidosis (e.g. hepatic failure)
4. **Metabolic acidosis**—respiratory alkalosis.

One should suspect a mixed acid-base disturbance when the compensatory response falls outside the expected range.

PRINCIPLES OF FLUID AND ELECTROLYTE THERAPY

Deficit Therapy

It is mandatory to ascertain the pre-existing deficit, i.e. losses as in acute gastroenteritis/acute diarrhea and correct it as early as possible. Though it is best calculated based on weight loss, in practice (since baseline weight is usually not known), it is assessed on the bases of clinical signs such as sensorium, thirst, sunken eyes, skin pinch, etc. Table 16.3 lists World Health Organization (WHO) simplified assessment system.

Therapy needs to be by fluid, similar in composition and amount, the quantity and route of administration varying with severity of dehydration. Mild-to-moderate dehydration can easily be treated with ORS.

In case of severe dehydration (>10% in infants; >6% in older children), restoration of the intravascular volume as early as workable is important. For this goal, rapid IV infusion of isotonic saline or Ringer's lactate as boluses (1–3), calculated according to the estimated deficit, (say 20 mL/kg) is the standard recommendation. Over and above the IV boluses, the severely dehydrated child needs to administered fluids, 10 mL for each percentage of weight loss.

Additionally, the child also needs to receive fluids and electrolytes as replacement for the amounts lost in

normal day-to-day metabolism, i.e. maintenance fluids (as described vide infra) as well as fluids as replacement for ongoing losses of body fluids.

Maintenance Therapy

A relationship exists between child's weight and his daily energy and fluid requirements. On an average, fluid requirement is 100 mL/100 kcal/day. Simultaneous needs for sodium = 1–3 mEq/100 mL kcal and potassium = 1–2 mEq/100 kcal/day. A 5% dextrose assists in providing not only energy, but also safeguarding from ketosis and gross tissue catabolism.

Though no single maintenance fluid is an answer for all clinical situations, Isolyte P meets these conditions to a large extent. It provides N/5 (0.18%) sodium chloride, 5% glucose and 20 mEq/L of potassium chloride.

Normal saline (0.9%) is the next choice. Except diabetes insipidus, acute kidney injury and heart failure (situation in which fluid restriction is advisable), it can be administered as a safe maintenance fluid. Table 16.4 lists maintenance fluid requirements in children.

While on fluid therapy, it is mandatory to maintain homeostasis. Hence, all children on IV fluids should be monitored for:

- Weight
- Fluid balance
- Clinical parameters
- Biochemical parameters.

Replacement of Ongoing Losses

It is important to replace the ongoing losses (vomiting, diarrhea, suction, aspiration) by fluids that are similar in composition and volume.

FLUID THERAPY IN SPECIAL SITUATIONS

Diarrheal Dehydration

This has already been briefly described in this very Chapter under "Principles of Fluid and Electrolyte Therapy". Also, See Chapter 29 (Pediatric Gastroenterology).

Table 16.3: Assessment of diarrheal dehydration as per WHO

Area of clinical observation	Actual observation(s)		
	No dehydration	Some dehydration	Severe dehydration
Look at			
General condition	Unconscious	Well, alert	Restless, irritable
Eyes	Sunken	Normal	Sunken
Tears	Absent	Present	Absent
Mouth and tongue	Dry	Moist	Dry
Thirst	Drinks poorly/unable to drink	Drinks normally, not thirsty	Drinks eagerly, thirsty
Feel			
Skin pinch	Goes back very slowly	Goes back quickly	Goes back slowly
Decide			
	The patient has No signs of dehydration	Two or more signs denote "some dehydration"	Two or more signs denote "severe dehydration"
Treat urgently	Use treatment Plan A	Use treatment Plan B	Use treatment Plan C

Table 16.4: Holliday-Seger formula for maintenance fluid in infants and children

Weight range	Daily fluid requirement
Upto 10 kg	100 mL/kg Rate/hour: 4 mL/kg
10–20 kg	First 10 kg 1000 mL + 50 mL/kg for each subsequent kg Rate/hour: 40 mL, 2 mL/kg for each subsequent kg
More than 20 kg	1500 mL + 20 mL/kg for each subsequent kg after 20 kg Rate/hour—60 mL + 1 mL/kg for each subsequent kg after 20 kg.

Malnutrition

- The characteristic features of dehydration accompanying protein energy and malnutrition (PEM) are:
 - It is difficult to evaluate it because of pre-existing loss of subcutaneous fat in marasmus and presence of edema in kwashiorkor.
 - It has a tendency to be hypertonic with low potassium.
- ORS is the therapy of choice in mild-moderate dehydration in PEM.
- In order to provide less sodium and more potassium, a special rehydration solution for severely malnourished child (ReSoMal) is recommended by the WHO (Table 16.5).

It may be prepared by dissolving a pack of standard ORS in 2 liters rather than 1 liter of water and adding sucrose 50 g and mineral mix solution 50 g.

Recommended regimen for ReSoMal is 75–100 mL/kg in 12 hours. It may be given orally or through nasogastric tube.

Intravenous fluid therapy is usually needed in severe dehydration in malnourished child:

- Initially, Ringer lactate or N/2 saline in 5% dextrose, 30 mL/kg in 2 hours
- Then, N/6 saline in 5% dextrose, 100 mL/kg in next 10 hours
- N/6 saline in 5% dextrose at half the rate in subsequent 12 hours
- Maintenance fluid, 75 mL/kg/day, may be continued until feeding is established
- It is advisable to add potassium to IV fluid after the child has passed urine.

Table 16.5: Composition of ReSoMal compared to standard ORS and hypoosmolar ORS (mmol/L)

	ReSoMal	Standard (ORS)	Hypo-osmolar (ORS)
Sodium	45	90	75
Potassium	40	20	20
Chloride	70	80	65
Citrate	7	10	10
Magnesium	3	–	–
Zinc	0.3	–	–
Copper	0.045	–	–
Total osmolarity	300	311	245

Abbreviation: ORS, oral rehydration salt/solution.

Acute Kidney Injury (AKI) (Acute Renal Failure)

- In order to be sure if the AKI is prerenal or intrinsic, fluid challenge is warranted. For this, a bolus of normal saline (which is similar to ECF) is given rapidly in a dose of 10 mL/kg. In prerenal AKI, higher urine output more than 1 mL/kg/hour follows.
- If the challenge turns out to be negative, another bolus of IV infusion along with frusemide, 2 mg/kg is given. If this too fails to increase the urine output, the diagnosis of intrinsic AKI stands confirmed.
- Management of intrinsic AKI revolves around restriction of fluid intake to insensible losses plus preceding day's urine output. The recommended fluid is plain dextrose (which is electrolyte-free), around 45–55 mL/kg/day (insensible losses 45 mL + urine output 10 mL/kg/day).

Heart Failure (Congestive Cardiac Failure)

The characteristic features of heart failure are:

- Fluid overload which demands fluid restriction to 2/3rd of the normal requirement.
- Hyponatremia from dilution and diuretic losses which does not demand increased sodium intake in view of the risk of worsening heart failure.
- Hypokalemia from diuretic usage/losses which demand correction.
- The recommended maintenance fluid is 70 mL/kg/day N/5 in 5% dextrose with 2 mL KCl/100 mL. This provides restriction to 2/3rd volume with extra potassium but normal sodium. Also, See Chapter 27 (Pediatric Cardiology).

Pyloric Stenosis

- Nonbilious progressive vomiting, often projectile and occurring soon after a feeding usually after 3 weeks of age, results in hypochloremic metabolic alkalosis. This is the hallmark of hypertrophic pyloric stenosis.
- Correction of dehydration and metabolic alkalosis before surgery is mandatory. Else, the infant is likely to develop postoperative apnea from anesthesia.
- Invariably, the infant responds to administration of saline (isotonic or 1/2 isotonic) infusion with added potassium.
- Occasionally, metabolic alkalosis refractory to this therapy may need ammonium chloride or arginine hydrochloride infusion.

Intestinal Obstruction

- The gastric juice contains around 60 mEq/L sodium, 10 mEq/L potassium and 85 mEq/L chloride. The ileal fluid contains over double sodium (130 mEq/L), same potassium (10 mEq/L) and more chloride (115 mEq/L).
- It is important to reduce the increasing abdominal distention by decompressing the stomach via an indwelling nasogastric tube. N/2 or N/3 saline (plus potassium) should be employed to replace the nasogastric aspirate, volume for volume.

- 262 ■** In case of an ileostomy, subsequent losses should be replaced with Ringer lactate (volume for volume).

Burns

- **Deficit:** Fluid replacement in burns in children more than 10 year of age is calculated as per the Parkland formula as follows:

Ringer lactate (mL) = weight (kg) \times 4 \times Percent TBSA

- **Maintenance:** Maintenance fluid therapy too is required as per the standard norms.

Pending calculated replacement, a beginning should be made with any delay with Ringer lactate or normal saline, 20 mL/kg/hour. Maintaining a urine output of 0.7–1 mL/kg/hour is a good monitoring.

Multiple Choice Questions

- All of the following observations are correct, except:
 - Intracellular fluid volume represents 50% of body weight
 - Important cations are sodium, potassium, calcium and magnesium
 - Important anions are chloride, bicarbonate, sulfate, organic acids and protein acids
 - It is important to replace ongoing losses (vomiting, diarrhea, suction, aspiration) by fluids that are similar in composition and volume
- All of the following drugs may cause high ADH secretion, except:
 - Narcotics
 - Analgesics
 - Nitazoxanide
 - Acetylcholine
- Spot the wrong observation about sodium:
 - Gastrointestinal tract (GIT) is the main organ involved in regulation of sodium balance
 - Maximum absorption occurs from GIT
 - Salt craving may point to the diagnosis of salt-wasting syndromes
 - In the human body, most of it is in exchangeable form
- What is not true about potassium?
 - It is the major intracellular cation with as high as 90% being exchangeable
 - Both renal and extrarenal mechanisms play a role in regulation of its balance
 - Insulin suppresses its uptake by the cell by directly stimulating sodium-potassium-ATP-ase activity
 - Its functions include excitability of nerve and muscle tissues
- Pick up the wrong observation:
 - Acute respiratory acidosis may follow airway obstruction
 - Mild metabolic alkalosis does not need any specific treatment
 - Cheyne-Stokes breathing occurs in severe metabolic acidosis
 - Respiratory alkalosis may result from salicylate intoxication

Answers

1. A 2. C 3. A 4. B 5. C

Clinical Problem-solving

Review 1

A 5-year-old girl presents with progressively increasing abdominal distention and generalized weakness. She has been taking furosemide tablets prescribed by a RMP for suspected puffiness of the eyes over the past few days. Auscultation shows absence of abdominal sounds. Ultrasonography reveals multiple fluid levels in abdomen.

- What is the most likely cause of her abdominal problem and generalized weakness?
- Why has this occurred?
- Could this complication be prevented?

Review 2

GK, aged 12 years, a known case of central *diabetes insipidus* as a sequelae of adequately treated *tuberculous meningitis* several years ago, presents with tough and doughy skin and subcutaneous tissue, irritability, lethargy, confusion and twitching. During the course of physical checkup, he develops generalized tonic-clonic seizures which responded to IV diazepam.

contd...

1. What is the most likely cause of the stated symptoms and signs?
2. A single test that is mandatory for establishing the diagnosis?
3. How to treat such a patient?

Answers

Review 1

1. Paralytic ileus which is supported by increasing abdominal distention, absent abdominal sounds and multiple fluid levels on imaging.
2. Excess diuresis from frusemide is known to cause hypokalemia which may cause paralytic ileus.
3. Yes, iatrogenic hypokalemia following frusemide therapy is a preventable condition. All that is needed to be done is to give supplements of potassium salt with frusemide. Alternatively, aldolactone (spironolactone) may be given along with frusemide.

Review 2

1. Hypernatremia resulting from excess loss of fluids as a result of *diabetes insipidus*.
2. Serum sodium which is likely to be >150 mEq/L.
3. If serum sodium is between 150–180, it needs to be brought down <145 mEq/L. This is attained by ensuring slow correction of hypernatremia, not more than 0.5 mEq/L/hour or 10 mEq/L/day fall. If level >180 mEq/L, peritoneal dialysis may well be the need. It is appropriate to correct associated hypocalcemia as well.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

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SECTION 3

Neonatology

Section Outline

17. Neonatology

INTRODUCTION

First 28 days of life after birth are described as newborn period. Proper care of the newborn babies forms the foundation for the subsequent life, not only in terms of longevity or survival, but also in terms of qualitative outcome without any mental and physical disabilities.

NOMENCLATURE/DEFINITIONS RELATED TO PERINATAL/NEONATAL PERIOD

Box 17.1 lists the noteworthy definitions concerning the prerinatal/neonatal period.

IMPORTANCE OF NEONATAL CARE

Currently infant mortality rate (IMR) at national level is around 36 per 1000 live births. Neonatal mortality rate (NMR) and perinatal mortality rate (PMR) are 24 and 20, respectively, per 1000 live births. Thus, a huge chunk of IMR is contributed by NMR and PMR. As shown in (Fig. 17.1), etiology of neonatal mortality revolves around:

- **Prematurity/low birth weight (LBW)/intrauterine growth retardation (IUGR):** 33%
- **Infections, including pneumonias and sepsis:** 33%
- **Birth asphyxia:** 20%
- **Congenital anomalies/malformations:** 10%
- **Miscellaneous:** 4%

Clearly a trio of prematurity/LBW/IUGR, serious infections and birth asphyxia accounts for as high as 85–90% of the neonatal mortality. Congenital malformations are responsible for nearly 10% deaths. Miscellaneous conditions share a meager 4% of the canvas. For achieving further reduction in IMR, it is imperative that we resort to urgent measures for improving the newborn care to bring down NMR.

NEONATAL MORTALITY AND MORBIDITY PATTERN: OVERVIEW

- **Prematurity and LBW**, responsible for about 1/3rd of neonatal deaths, are also discussed subsequently in this very Chapter.
- **Serious neonatal infections**, also responsible for around 1/3rd of neonatal deaths, include congenital infections (T)oxoplasmosis, (O)ther agents, (R)ubella, (C)ytomegalovirus and (H)erpes simplex (TORCH) and acquired infections such as sepsis and pneumo-

Box 17.1

Noteworthy definitions in relation to the neonate

- **Neonatal period:** First 28 days after birth
- **Early neonatal period:** First 7 days of life
- **Late neonatal period:** More than 7th–28 days of life
- **Perinatal period:** From 28th week of gestation (or over 1000 g of birth weight) to 7th day of life
- **Extended perinatal period:** From 22nd week of gestation (or over 500 grams of birth weight) to 7th day of life
- **Term baby:** Neonate born between 37 weeks (completed) and 42 weeks (completed) of pregnancy, irrespective of the birth weight
- **Preterm baby:** Neonate born before 37 weeks (completed) or less than 259 days irrespective of birth weight
- **Post term baby:** Neonate born after 42 weeks (completed) or more than 294 days irrespective of birth weight
- **LBW:** Birth weight less than 2500 g, irrespective of gestational age
- **VLBW:** Birth weight less than 1500 g, irrespective of gestational age
- **ELBW:** Birth weight <1000 g, irrespective of gestational age
- **SGA or SFD:** Birth weight less than 10th percentile for that period of gestation
- **LGA or LFD:** Birth weight more than 90th percentile for that period of gestation
- **AGA:** Birth weight between 10th and 90th percentile for that period of gestation
- **Live born:** Product of conception that shows an evidence of life (breathing, heartbeat, pulsation of umbilical cord or definite movements of voluntary muscles) after separation from the mother
- **Still born:** (late fetal death) is a product of conception that fails to show an evidence of life, (breathing, heartbeat, pulsation of umbilical cord or definite movements of voluntary muscles), provided that gestational age is 22 weeks or more or weight exceeds 500 g. Such a baby is expected to have been alive in utero and died during passage through the birth canal.

Abbreviations: LBW, low birth weight; VLBW, very low birth weight; ELBW, extremely low birth weight; SGA, small for gestational age; SFD, small for date; LGA, large for gestational age; LFD, large for date; AGA, appropriate for gestational age.

nias. These are described in details later in this very chapter.

- **Perinatal asphyxia**, responsible for nearly 1/5th neonatal deaths, is known to cause in the survivors such as long-term sequelae such as, impaired attention span, hyperactivity, epilepsy, mental retardation, bulbar and pseudobulbar palsies and auditory deficits. The topic is discussed under hypoxic-ischemic encephalopathy elsewhere in this very Chapter.
- **Birth trauma (Figs 17.2 to 17.4)**, more important from the angle of morbidity, may cause fracture of skull,

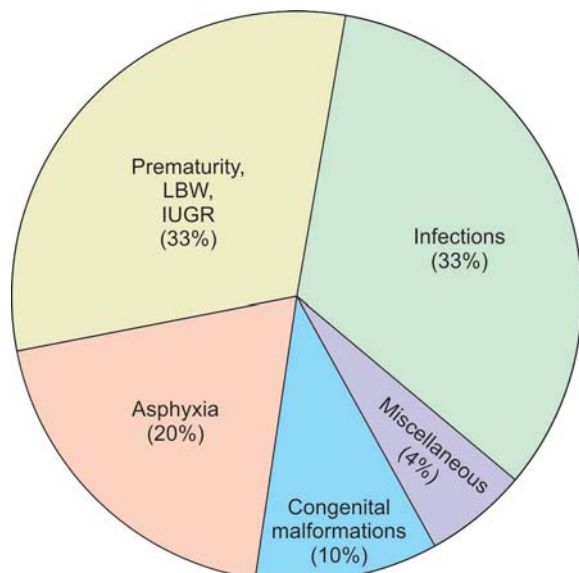


Fig. 17.1: Histogram showing current pattern of neonatal mortality in India. Abbreviations: LBW, low birth weight; IUGR, intrauterine growth retardation/restriction.

clavicle and extremities and various paralysis such as Erb paralysis (due to involvement of fifth and sixth cervical roots), Klumpke paralysis (due to involvement of eighth cervical and first thoracic roots with or without injury to cervical sympathetic plexus) and facial palsy (due to seventh nerve paralysis). Breech extraction may cause fracture of a long bone.

- **Sternomastoid tumor** may occur in difficult breech deliveries in particular.
- **Intracranial hemorrhage** is a serious condition in which hemorrhage occurs in the cranial vault. Depending on the site it may, for example, be intraventricular hemorrhage (IVH), subarachnoid hemorrhage or subdural hemorrhage.
- **Cephalhematoma** is rather benign, self-limiting and resolves in a few weeks' time. The swelling is nonpul-



Fig. 17.3: Facial palsy. There was history of birth trauma.



Fig. 17.2: Erb paralysis. Note the characteristic position of the left arm which is adducted and internally rotated with pronation of the forearm. The cause is injury to the 5th and 6th cervical nerves.

satile, does not increase in size on crying and does not cross a suture line (Fig. 17.5). The most common site is the parietal or occipital bone. It needs no treatment.

- **Caput succedaneum**, resulting from molding, consists of serosanguinous fluid collection over the presenting part between the pericranium and the scalp tissue. It is present at birth, crosses the suture line and disappears within a few hours to a day or so (Fig. 17.6).
- **Congenital malformations and other defects** (Figs 17.7 to 17.18) may hamper newborn's survival. These include congenital heart disease, choanal atresia, omphalocele (bowel and other viscera herniating through a defect in the abdominal wall), congenital diaphragmatic hernia (CDH), tracheoesophageal fistula (TOF), intestinal obstruction, anorectal anomalies, Pierre Robin syndrome (micrognathia, i.e. a small mandible,



Fig. 17.4: Fracture of the left femur following breech.



Fig. 17.5: Cephalhematoma. The lesion is soft and fluctuating. Since it is subperiosteal, it does not cross a suture lines.

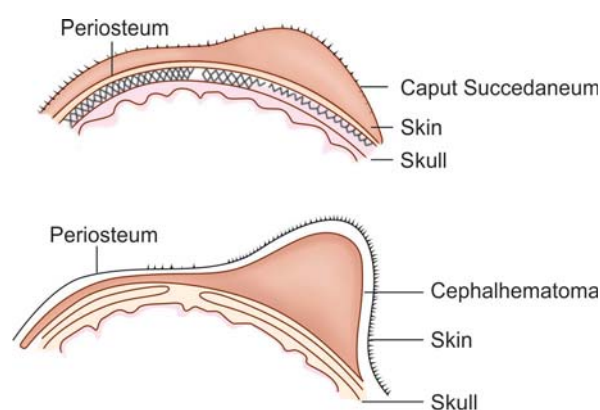


Fig. 17.6: Development of caput succedaneum and cephalhematoma. Caput succedaneum: serosanguinous fluid collection in the soft tissue, not limited by suture lines, disappears speedily. Cephalhematoma: Collection is blood, between skull bone and overlying pericranium, limited by suture line; disappears slowly in a few weeks.



Fig. 17.7: Dysmorphic facies. Note the remarkably depressed bridge of nose.

cleft palate and posterior displacement of tongue) and neural tube defects (NTDs) such as meningocele (spina bifida with herniation of meninges, nerve roots and spinal cord). Immediate recognition of such



Fig. 17.8: Extroversion of cloaca.



Fig. 17.9: Congenital diaphragmatic hernia. Note the abdominal contents herniated into thorax.



Fig. 17.10: Pierre Robin syndrome. Note the shrew like facies due to hypoplastic mandible (micrognathia), glossoptosis and high-arched cleft palate.

anomalies is important. These conditions are discussed elsewhere in different chapters.

A careful examination may also help early recognition of diseases such as congenital hypothyroidism, Cushing syndrome, Down syndrome and Turner syndrome.



Fig. 17.11: Frontal encephalocele. The sac contains both meninges and brain in about 2/3rd patients with encephalocele, there is accompanying hydrocephalus that may be detected only on CT scan.



Fig. 17.14: Microcephaly with herniation of brain tissue.



Fig. 17.12: Occipital encephalocele. The swelling fluctuates in size with coughing or crying which alter the intracranial pressure. Note that this stillborn baby also had anencephaly and hemicrania, the defects that are known to be incompatible with life.



Fig. 17.15: Anencephaly. In this infant, who died within 24 hours of birth, membranous skull as well as cerebral hemisphere were absent.



Fig. 17.13: Occipital encephalocele. It needs to be differentiated from cranial meningocele by palpation, transillumination and, if needed, CT scan.



Fig. 17.16: Meningocele. The swelling, containing primarily meningeal tissue, shows good transillumination and no significant functional disability. In order to safeguard against infection and perforation, immediate surgical excision is recommended.



Fig. 17.17: Meningomyelocele. A relatively higher site, poor transillumination and neurologic deficit are the hallmarks of this anomaly.



Fig. 17.18: Spina bifida occulta. Abnormal tuft of hair in an infant with radiologically proven underlying spina bifida occulta. Besides hair tuft, other conditions that should arouse suspicion of spina bifida occulta include telangiectasia and subcutaneous lipoma. The anomaly is most common at L5 and S1, but it may involve any portion of the vertebral column.

NEONATAL RESUSCITATION PROGRAM (NRP)

Around 10% newborns need some resuscitation to begin breathing at birth. Understandably, neonatal resuscitation is a real emergency, requiring participation of everyone in the labor/delivery room. The fact that 70% of the babies with absent heart beat can be resuscitated shows how rewarding the maneuver is. Often a good antenatal check-up indicates whether resuscitation is likely to be needed. A weak fetal heart of less than 100 beats/minute or its irregularity during the late stage of labor is a sign of progressive asphyxia that will need resuscitative measures.

Currently, globally, the trend is to follow the Neonatal Resuscitation Program (NRP) based on the American Heart Association (AHA) and American Academy of Pediatrics (AAP) Guidelines which are duly endorsed by the International Liaison Committee on Resuscitation. In India, The National Neonatology Forum (NNF) and the Indian Academy of Pediatrics are aggressively propagating these guidelines through Neonatal Advanced Life Support (NALS) Course workshops across the country. Though 2010 guidelines are in vogue, updates from 2015 guidelines (given towards the end of the description on NRP need to be incorporated in practice).

High-risk Situation

- **Maternal:** The situations in relation to **high-risk pregnancy** in which the mother is suffering from an adverse factor, e.g maternal malnutrition, bad obstetrical history, hypertension, rhesus (Rh) isoimmunization toxemias, etc.
- **Fetal:** Preterm birth, LBW infants, multiple pregnancies, fetal malformations (identified on ultrasonography), IUGR, fetal distress manifested by certain signs (meconium-stained liquor amnii, abnormal variation in fetal heart rate or rhythm, electrocardiogram {ECG}) changes in fetal monitoring records, changes in fetal blood pH and gases on fetal blood samples).

The Golden Minute Concept

According to this concept, if by the end of one minute of initial steps directed at stabilization, satisfactory outcome is not forthcoming, assisted ventilation becomes mandatory. Once positive pressure ventilation or supplementary oxygen administration is begun, assessment should consist of simultaneous evaluation of three vital characteristics, namely **heart rate, respiration** and **the state of oxygenation** rather than the color (earlier criterion). Oxygenation is optimally determined by pulse oximeter.

Initial Rapid Assessment: Whether Resuscitation Needed or Not?

As per new guidelines, the following three questions need to be answered in the initial assessment;

1. Is this a term gestation?
2. Is the infant crying and breathing?
3. Does the infant have good muscle tone?

The previous guidelines included the question *Is the amniotic fluid clear of meconium and evidence of infection?* which stands deleted in the new guidelines.

In case answer to all these three questions is *yes*, the infant is not in need of any resuscitation. If it is *no* to any of the questions, the infant is in need of initial steps in stabilization which too are a part of resuscitation.

Resuscitation Equipment

It should be obligatory on the part of each and every delivery room to maintain an easily accessible neonatal resuscitation tray which is cross-checked and replenished from time to time (Box 17.2).

Box 17.2

Checklist of neonatal resuscitation equipment and supplies

- **For suction:** Mucus aspirator, meconium aspirator, mechanical suction, suction catheters 10 F or 12 F, feeding tube 6 F, 20 mL syringe.
- **For bag and mask ventilation:** Neonatal resuscitation bag, face masks (fullterm and preterm sizes), oxygen with flowmeter and tubing.
- **For endotracheal intubation:** Endotracheal tubes 2.5, 3.0, 3.5, 4.0 and 1 D, laryngoscope with straight blades of size 0 (preterm) and 1 (term) with extra batteries and bulbs for laryngoscopy, stylet, scissors.
- **Medications:** Epinephrine, normal saline, sodium bicarbonate, naloxone and sterile water.
- **Miscellaneous:** Radiant warmer, umbilical catheters, watch with seconds hand, linen and shoulder roll, stethoscope, adhesive tape, syringes 1–50 mL, gauze and 3-way stopcock gloves.

Adequate Preparation for Resuscitation

Every delivery warrants availability of:

- A radiant warmer ready for use
- All resuscitation equipment immediately available and in good working order
- At least one trained person (preferably two) skilled in neonatal resuscitation.

TABC of Resuscitation: Initial Steps in Stabilization

- **T—Temperature:** Maintenance of warmth is achieved by:
 - Placing the neonate under a preheated radiator warmer or, alternatively, overhead 200 Watt bulb/room heater.
 - Drying the neonate as soon as he is placed under the warmer using a prewarmed towel.
 - Removing the wet towel and replacing it with a dry and prewarmed one.

Over and above the maintenance of temperature, the major steps in neonatal resuscitation follow the time-honored ABC (Airway, Breathing, Circulation) pattern and should be completed as far as possible within 15 seconds of birth.

- **A—Airway:** Anticipate and establish an open airway by:
 - Positioning of the neonate.
 - Suction of mouth, nose and, at times trachea.
 - Performing endotracheal intubation and aspiration.
- **B—Breathing:** Tactile stimulation such as slapping the foot, rubbing the back, etc or positive pressure ventilation (PPV) with a bag and mask or through an endotracheal tube
- **C—Circulation:** Maintain the circulation with:
 - Chest compression and
 - Medications, if needed.

Opening the Airway

- **Positioning:** The neonate should be placed on his back/ side with the neck slightly extended to straighten the airway and head kept slightly down to prevent aspiration with a shoulder roll made out of a towel or a blanket.

- **Suction:** If no meconium is present, first the mouth and oropharynx and then the nose and nasopharynx should be gently suctioned. If there is meconium-stained amniotic fluid, suction should be done when head is delivered but shoulders are yet to be out. This is termed **intrapartum suctioning**. After the delivery of the infant, residual meconium in the hypopharynx should be suctioned out under direct vision laryngoscopy.

Initiating Breathing

- **Tactile stimulation:** If the depressed baby fails to have respiration despite drying and suctioning, additional tactile stimulation may be provided by slapping or flicking the soles of the feet and rubbing the back firmly once or twice.
- **Positive pressure ventilation (PPV):** If the baby is still depressed (apnea, heart rate less than 100/minute), he should be administered free-flow oxygen (bag and mask ventilation) as per Box 17.3 and Fig. 17.19. If it fails, endotracheal intubation should be performed.
- **Endotracheal intubation:** It is done after the baby is delivered to remove secretions from the lower airway. It is indicated in all babies who are depressed and meconium stained (Box 17.4, Figs 17.20 and 17.21).

Box 17.3

Bag and mask ventilation

Indications

- Apnea/gasping
- Heart rate less than 100/minute.

Equipment

- Resuscitation bag (self-inflating, capacity 240–260 mL) (Fig. 17.21)
- Oxygen (90–100%)
- Masks (well fitting, cushioned)
- Oxygen equipment (source, flow meter, tubing, etc).

Procedure

- The baby's neck should be slightly extended to ensure an open airway while he lies on his back. An appropriate-sized bag and mask is selected.
- The mask is placed in position so that it covers the mouth and the nose, but not the eyes. Then, bagging is started at a rate of 40–60/minute for 15–30 seconds, using enough pressure to cause chest movements.

Evaluation

- If heart rate is more than 100/minute and infant having spontaneous breathing, stop bagging (ventilation).
- If heart rate more than 100, but infant yet not having spontaneous breathing or is gasping continue ventilation.
- If heart rate 60–100/minute and not increasing, continue ventilation and check for adequacy of ventilation from chest elevation.
- If heart rate 60–100/minute and increasing, continue ventilation.
- If heart rate less than 80/minute, start chest compressions.
- If heart rate less than 60/minute, continue to ventilate, start chest compressions and consider intubation.

Signs of improvement:

- Rising heart rate
- Spontaneous breathing
- Improving color.

Risks

Abdominal distention because of gastric distention from entry of air into stomach during ventilation exceeding 2 minutes.

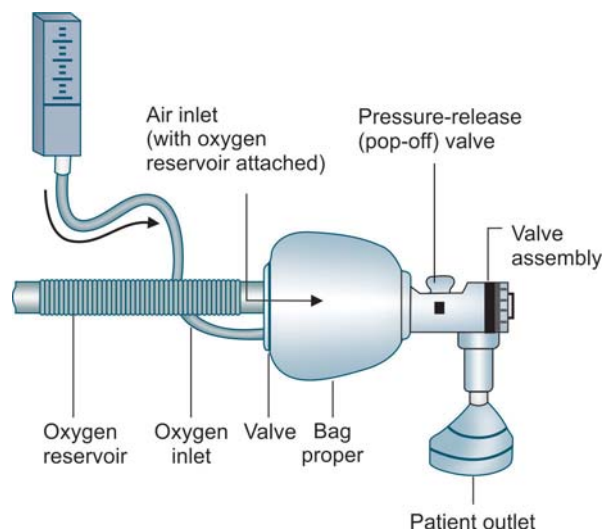


Fig. 17.19: Self-inflating bag. A 250–750 mL size bag comprising of 4 major components (inlet, bag proper, patient outlet and O₂ reservoir) is appropriate for a neonate. The most often employed gadget is ambulatory/artificial manual breathing unit (AMBU).

Box 17.4 Endotracheal intubation (Figs 17.20 to 17.22)

Indications:

- Failure of bag and mask ventilation as well as medication
- When PPV is needed
- When tracheal suction, especial for aspiration of meconium, is needed
- Diaphragmatic hernia.

Equipment

Endotracheal tube of appropriate size, neonatal laryngoscope with straight blades of size 0 for preterms and 1 for term babies.

Procedure

- The newborn is placed on a resuscitation table (high enough and with flat surface) in a supine position with fully extended neck at the edge of the table. It is good to place folded towel or blanket beneath the shoulders to facilitate this position.
- The operator sits on a stool at the head end. As he opens the infant's mouth with the index finger and the thumb of the right hand, his left hand introduces the lighted laryngoscope (infant size) into the nasopharynx upto the epiglottis.
- The glottis is cleared by gentle suction. This makes it easier to clearly see the epiglottis and the surrounding structures. When the glottis is visible, a curved endotracheal tube is gently inserted through the larynx. Make sure that it is not pushed too far to prevent its entry into the right bronchus. The laryngoscope is now withdrawn.
- The IPPR is given through the tube either by simply puffing in air from operator's mouth or with a bag or mechanical respirator.
- As soon as respiration gets established, the tube should be withdrawn. If the response is poor, still efforts have got to be continued as long as the heart beat exists.

Precautions during intubation

In order to prevent hypoxia during intubation, provide free flow oxygen, limit intubation attempt to 20 seconds and avoid excessive flexion of neck.

Precautions during extubation:

- Give free-flow oxygen through the lid of the endotracheal tube for a few seconds.
- Always take help of a laryngoscope during extubation.
- Continue bag and mask ventilation for 15 seconds after extubation.

Abbreviations: IPPR, intermittent positive pressure respiration; PPV, positive pressure ventilation.

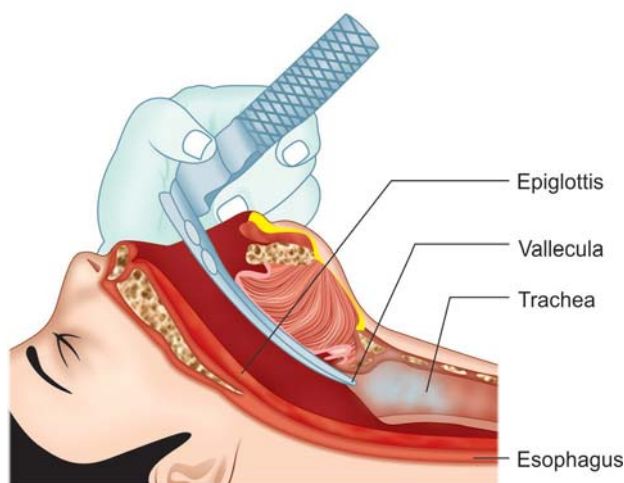


Fig. 17.20: Endotracheal intubation technique: Note the endotracheal tube in position. It is inserted upto 2.5 cm beyond the vocal cord.

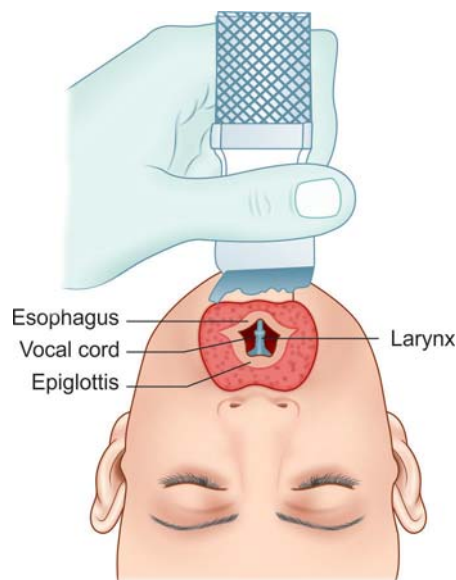
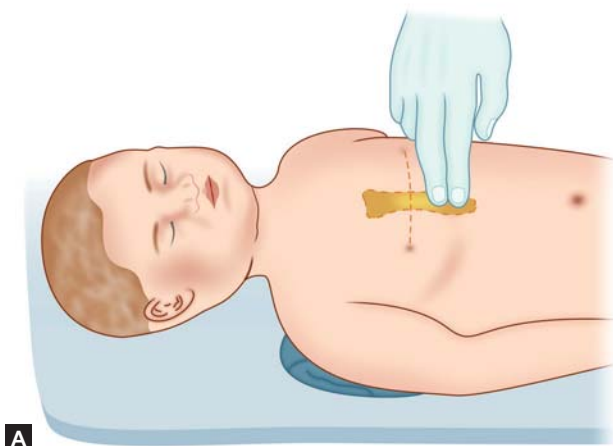


Fig. 17.21: Endotracheal intubation technique. The glottis (triangular opening formed by vocal cord and arytenoid cartilage) as viewed through laryngoscope.

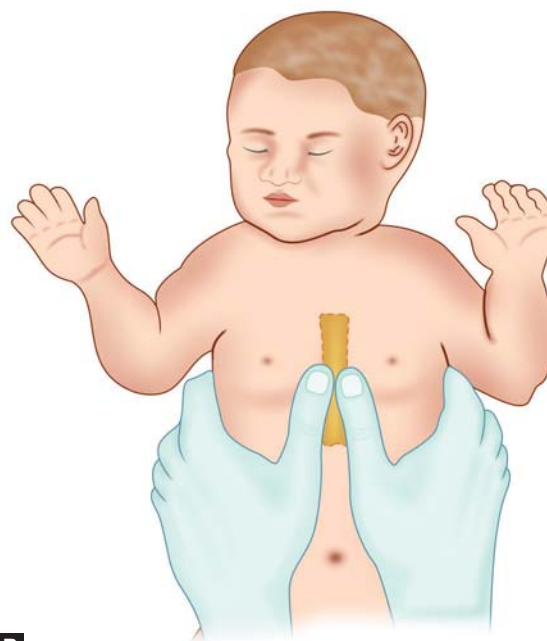
Maintaining Circulation

Chest compression (external cardiac massage) is given if heart rate remains less than 60/minutes. It consists of rhythmic compressions (120/minutes; ratio 3:1) of lower third of the sternum that compress the heart against the spine, raise the intrathoracic pressure and circulate blood to the vital organs (Figs 17.22A and B). Details are given in Box 17.5.

Medication is only rarely needed. Depressed neonates with heart rate less than 60/minutes despite adequate ventilation with 100% oxygen, air-oxygen mixture, or room air (the last two may be preferred) and chest compressions are candidates for receiving medication in the form of epinephrine, volume expanders, sodium bicarbonate and dopamine. There is no place for dexamethasone, atropine, mannitol, calcium, dextrose and naloxone in resuscitation in the delivery room.



A



B

Figs 17.22A and B: Chest compression. It consists of rhythmic compressions (120/min; ratio 3:1) of lower third of the sternum if heart rate remains <60/minute. **(A)** Two finger technique in which tips of the middle finger and an adjoining finger of a hand are employed to depress the lower 1/3rd of the sternum; **(B)** Thumb technique in which thumbs of both hands are employed to depress the lower 1/3rd of the sternum.

Box 17.5 Chest compression

Indications:

If after 15–30 seconds of positive pressure ventilation (PPV) with 100% oxygen, heart rate remains <60/minute or it is 60–80/minute, but not increasing.

Site:

Lower third of the sternum below the imaginary line drawn between two nipples.

Procedure:

In the thumb technique, thumbs are employed to compress the sternum while the fingers support the back and the hand encircles the torso. In the two-finger technique, the finger tips (middle finger with index finger or ring finger), one hand are employed to compress the sternum. The other hand supports the neonate's back. The rate of chest compressions should be 120 beats/minute and depth 1–2 cm. During the procedure, fingers of thumbs must never be taken off the sternum in between compressions.

Evaluation:

Thirty seconds of chest compression should be followed by rechecking of the heart rate. If it is below 80 beats/minute, the procedure should continue along with bag and mask ventilation with 100% oxygen, plus medication (vide text). If heart rate is more than 80/minute, stop chest compression but continue ventilation until heart rate crosses 100 beats/minute and the baby is breathing spontaneously.

Risks:

Trauma to the chest in the form of fractures, pneumothorax and laceration of liver.

- **Epinephrine A:** 1 in 10,000, 0.1–0.3 mL/kg intravenous (IV). Intratracheal (IT) is given rapidly. The same dose may be repeated every 5 minutes.
- **Volume expanders:** Normal saline, whole blood, 5% albumin or Ringer lactate is indicated in the event of an acute bleeding with signs of hypovolemia.
- **Sodium bicarbonate:** 1–2 mEq/kg/minute of 4.2% solution slowly over 2 minute period after effective

ventilation has been established. It is indicated only in the event of documented metabolic acidosis. Else, there is risk of such a therapy producing respiratory acidosis.

- **Dopamine:** 5–20 mg/kg/minute as a continuous IV infusion in poor peripheral perfusion, weak pulses, hypotension, tachycardia and urine output persisting after the initial resuscitative efforts.

In earlier guidelines, naloxone 0.01 mg/kg (IV, subcutaneous {SC}, intramuscular {IM}, IT) was recommended in case of history of maternal narcotic drug administration. New guidelines do not recommend naloxone.

Pulse Oximetry

The new guidelines have emphasized the use of pulse oximetry rather than the color of the baby (Box 17.6).

Supplementary Oxygen

The new guidelines stress the need for employing room air providing 21% oxygen (rather than using 100% oxygen) in both term and preterm infants for better survival. Initial resuscitation should, therefore be with air or blended oxygen. Oxygen concentration should be titrated to achieve

Box 17.6 Pulse oximetry

Pulse oximetry should be employed:

- When resuscitation is anticipated
- When positive pressure is administered for more than few breaths
- When cyanosis is persistent.
- When supplementary oxygen is administered.

The probe should be attached to a preductal location, i.e. right upper extremity, usually wrist or medial surface of palm. Attaching the probe to the infant before connecting the probe to the instrument facilitates the most rapid acquisition of signal.

Box 17.7**Paradigm changes in neonatal resuscitation as a result of 2010 guidelines of AHA/AAP**

- In rapid assessment immediately after birth, the stress on “*Is the fluid clear?*” stands omitted in new guidelines.
- Pulse oximetry rather than neonate’s color should be employed to assess need for oxygenation.
- Rather than 100% oxygen, room air (21% oxygen) should be used for resuscitation of term babies needing PPV.

Abbreviations: PPV, positive pressure ventilation; AHA, American Heart Association; AAP, American Academy of Pediatrics.

SpO₂ in target range. In case blended oxygen is not available, resuscitation should be initiated with air. If bradycardia is present, as indicated by heart rate less than 60 beats/minutes after 90 sec of resuscitation, oxygen concentration should be increased in increments to 100% until recovery of a normal heart rate.

For term infants on plasma volume variation (PVV) too, in the new guidelines there is a paradigm shift from 100%–21% oxygen. For preterm infants on PPV, 30–90% oxygen is recommended for initial resuscitation. Thereafter, it can be titrated to achieve the target Saturation of oxygen (SpO₂) values. Use of blended air oxygen mixture should be judicious and guided by pulse oximetry.

Continuous positive airway pressure (CPAP) in delivery room need not be for only preterm infants less than 32 weeks with respiratory distress. The new guidelines recommend CPAP for persistent cyanosis or labored breathing after initial steps.

Major Changes in 2010 NRP Guidelines by AHA/AAP

These are listed in Box 17.7.

Do not in Neonatal Resuscitation

These are listed in Box 17.8. As the baby starts breathing on his own, the endotracheal tube should be removed. Brushing the soles of the feet stimulates crying and is recommended. It is a sound principle never to leave a baby needing resuscitation until and unless he is crying well.

Salient Features of 2015 NRP Guidelines

- Order of the 3 assessment parameters is changed as follows: 1. Term gestation, 2. Good tone, 3. Breathing or crying.
- Delayed cord clamping for >30 seconds for both term and preterm infants who do not require resuscitation at birth.
- Hyperthermia must be avoided.
- Simple measures to prevent hypothermia in first hours of life (use of plastic wraps, skin-to-skin contact and even placing the infant after drying in a clean plastic bag up to the neck) may reduce mortality.
- Routine intubation for tracheal suction is no longer recommended.
- Assessment of heart rate remains critical during first minute of resuscitation. Hence, 3-lead ECG should

Box 17.8**Certain vital “do not” in neonatal resuscitation**

- Do not administer heavy sedation to the mother.
- Do not do heavy and continuous suction.
- Do not let the neonate develop hypothermia.
- Do not carry on with tactile stimulation beyond two and never beyond four flicks.
- Do not delay endotracheal intubation in an apneic neonate.
- Do not blow your lungs into neonate’s mouth.
- Do not use full palmar grasp for giving bag and mask ventilation.
- Do not give respiratory stimulants.
- Do not suck the nose first and the mouth later. The breathing effort that follows sucking the nose first may allow secretions in the mouth to be suddenly aspirated into the lower airway.
- Do not slap the back.
- Do not squeeze the rib cage.
- Do not force thighs on the abdomen.
- Do not dilate the anal sphincters.

be for heart rate monitoring, and pulse oximetry for oxygenation.

- Resuscitation of preterm newborns of less than 35 week gestation should be initiated with oxygen (21 to 30%) and oxygen titrated to achieve preductal oxygen saturation approximating the range achieved in healthy term infants.
- Spontaneously breathing preterm infants with respiratory distress may be supported with CPAP initially rather than with routine intubation for administering PPV.

Resuscitation steps of the 2015 guidelines are presented in Figure 17.23.

Apgar Score

First put forward by Prof Virginia Apgar, a renowned New York-based anesthesiologist, in 1953, Apgar score is a quantitative assessment of neonate’s condition at birth, especially with reference to the respiratory, circulatory and neurologic status (Table 17.1).

It is of no use for taking a decision regarding the steps of resuscitation. Reason: Resuscitation is needed within a minute, i.e. before the Apgar scoring is done.

Apgar scoring system is employed to plan management of the newborn after resuscitation has been accomplished. Contrary to the commonly-held belief, it has absolutely no role in deciding steps of resuscitation in the labor room. Interpretation of one minute score is categorized in Table 17.2 and that of later score and limitations of the scoring system in footnotes to the said table.

THE FULLTERM NEWBORN (BOX 17.9)

Physical Characteristics

- The normal fullterm newborn weighs around 3.4 kg (range 2.5–4.6 kg) and the length averages around 50 cm (range 45–55 cm).
- The head circumference is about 35 cm (range 32.6–37.2 cm).
- The chest circumference is approximately 3 cm less than the head circumference at birth. The chest is

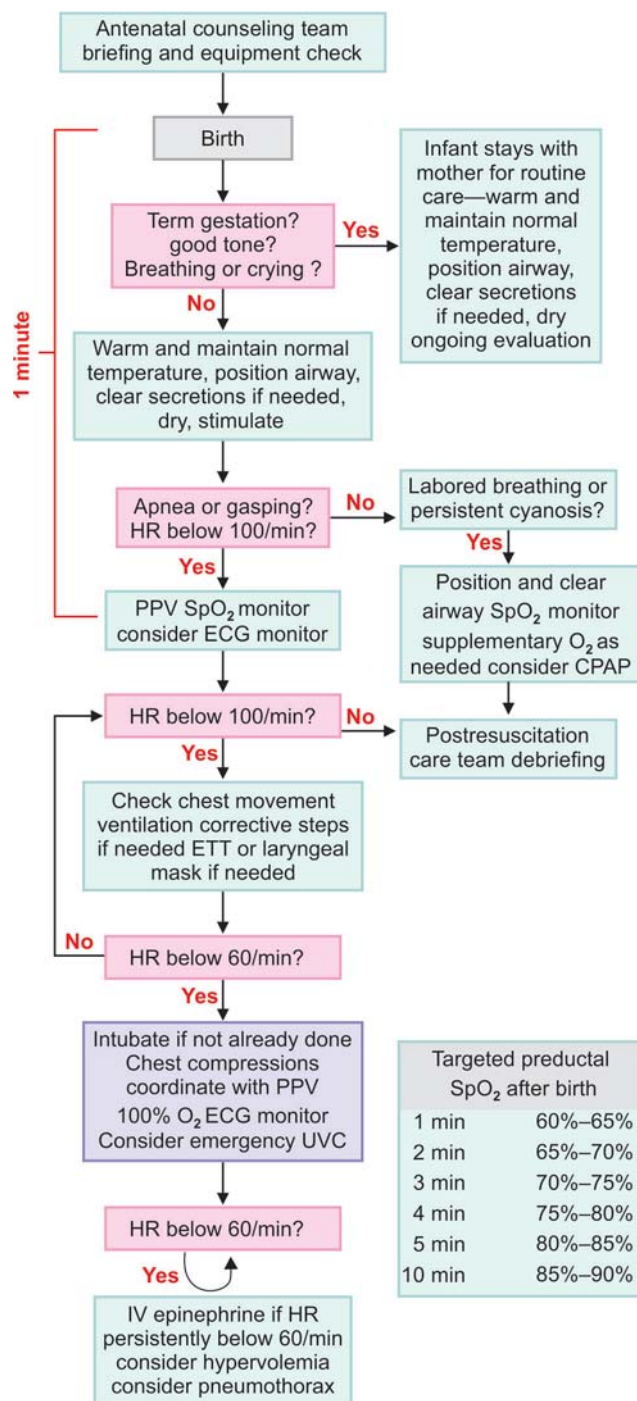


Fig. 17.23: Algorithmic approach to neonatal resuscitation as per American Heart Association/American Academy of Pediatrics recommendations of 2015.

Abbreviations: PPV, positive pressure ventilation; SpO_2 , oxygen saturation; HR, heart rate; ECG, electrocardiogram; ETT, exercise tolerance test; UVC, umbilical venous catheter; IV, intravenous; CPAP, continuous positive airway pressure.

rounded rather than flattened anteroposteriorly. The abdomen is prominent.

- The upper segment/lower segment ratio is 1.7:1. In other words the trunk is relatively larger and the extremities short. The midpoint of the length (stature), therefore, lies at the umbilicus instead of the symphysis pubis as in grown-up children and adults.

Table 17.1: Apgar scoring system

Clinical features	Score 0	Score 1	Score 2
Appearance (Color)	Blue or pale	Body pink, limbs blue	Pink all over
Pulse (Heart rate)	Nil	Less than 100 per minute	Over 100 per minute
Grimace (Response to catheter put into nostril or stimulation of sole of foot)	Nil	Grimace or feeble cry	Cry or sneezing
Activity and tone	Limp	Some flexion of limbs	Active movements
Respiration	Nil	Slow, irregular	Good, strong cry

Table 17.2: Interpretation of one minute Apgar score

Apgar score	Interpretation	Action needed
7–10	Excellent condition with no birth asphyxia	Needs no particular observation
4–6	Moderate birth asphyxia	May be shifted to mother but needs to be carefully observed
0–3	Severe birth asphyxia	Needs care in NICU

Abbreviation: NICU, neonatal intensive care unit.

Box 17.9

Noteworthy peculiarities of the fullterm neonate in nutshell

Anthropometry

- Weight—3.4 kg (2.5–4.6 kg)
- Length—50 cm (45–55 cm)
- Head circumference—35 cm (32.6–37.2 cm)
- Chest circumference—32 cm
- Upper segment/lower segment ratio (crown-rump/rump-heel ratio)—1.7:1
- Midpoint of length lies at umbilicus rather than at pubic symphysis.

Vitals

- Respiratory rate—40/min (35–50/min)
- Heart rate—140/min (120–160/min).

Hematologic status

Hemoglobin 18 g/dL.

Miscellaneous

- Posture is of partial flexion
- Palpability of liver and spleen is usual
- Palpability of kidneys may be present in some
- Sinuses are small and underdeveloped
- Only solitary mastoid cell in antrum
- Eustachian tube is short and broad. Ear drum placed more obliquely
- External auditory canal short and straight.

- The newborn's posture is a prototype of the partial flexion attitude in utero.
- The external auditory canal is relatively short and straight and the eardrum thick. The Eustachian tube is short and broad. The mucoid material in the middle ear may simulate an exudate of infection.
- The maxillary and ethmoid sinuses are small. The frontal and sphenoidal sinuses are poorly developed.
- The kidneys are often palpable; so are the liver and spleen just below the costal margins.

- The traumatic effects of labor may be encountered in the form of edema of the vertex and overriding of the cranial bones, especially parietal over occipital and parietal.
- The pinkish or mottled skin on the dorsal aspects of extremities and upper back is covered with lanugo hair.
- The sclerae tend to be somewhat bluish. The ear cartilage is fully curved and firm, showing quite good elastic recoil.
- The breast nodule is palpable, measuring over 5 mm in diameter.
- The scrotum shows adequate rugae and deep pigmentation. At least one testis is fully palpable in the scrotum.
- The labia majora covers the labia minora.
- The sole of foot shows prominent deep creases in anterior 2/3rd or more area.

Physiological Characteristics

- The established respiratory rate varies between 35 and 50/minute. Crying tends to enhance the rate upto 60/minute. Peripheral cyanosis may be encountered for a short while after birth.
- The heart rate varies between 120 and 160/minute. Besides high cardiothoracic ratio as compared to an adult, transient benign murmurs are often heard.
- The cry is, as a rule, vigorous.
- Rooting (turning the head towards and to root about a stimulus placed close to the mouth), suckling, gagging and swallowing reflexes are well developed. The newborn is, therefore, capable of accepting breastfeeding within a few hours following delivery when the recovery from exhaustion of birth is over.
- The initial demand for feed at irregular intervals gives way, by the end of the first week, to a fairly regularized pattern of demand at 2–5 hours.
- The first stools (meconium) are passed within 24 hours and are black-colored, thick and viscid. On third to fourth day, these are replaced by greenish-brown stools with milk curds, the so-called **transitional stools**. After another gap of 3–4 days, typical milk stools follow.
- The first urine is passed during or shortly after birth. A proportion of the newborns may take 24 hours or even longer (upto 48 hours) to pass urine. Failure to pass urine by 48 hours is a matter of concern.
- The output and glomerular filtration rate (GFR) show rapid increase in the first two weeks. Abundance of urates gives the diaper a pink stain.
- The body temperature quickly falls after birth, but is reverted within 4–8 hours.
- The energy requirements initially are 55 kcal/ kg/ day, but rise to 110 kcal/kg/day by the end of the first week.
- On an average, the term newborn loses about 6% of body weight during the first week. The weight loss may be upto 10% (upto 15% in preterms). If the loss is in excess of 10%, dehydration fever on the third to fourth day may develop. The initial weight loss is made up by the tenth day.
- The hemoglobin is high (around 18 g/dL) with slight reticulocytosis, normoblastemia and leucocytosis (upto 35,000/mm³) on first couple of days after birth. Notably, stressful situations (say fulminant infections) may cause only negligible leucocytosis and even leukopenia.
- Establishment of normal homeostatic mechanism depends on acquisition of normal intestinal flora and elaboration of vitamin K rather than on minimal passage of clotting factors from the mother.
- Blood sugar is relatively low in the newborn and a fall below 20 mg/dL may cause seizures. Likewise, blood calcium is low and a fall below 7.5 mg/dL may lead to seizures.
- Though immunoglobulins (Ig)G level of the newborn is quite high, the IgM, IgA and IgE levels are negligible. Near absence of IgM in the newborn predisposes him to Gram-negative bacillary infections. T-lymphocyte functions too are reduced in the neonate.
- Fat is not as efficiently digested by the newborn as protein and carbohydrates.
- At cellular level, red cells are more vulnerable to hemolysis. There is greater risk of unconjugated hyperbilirubinemia and enhanced risk from drug therapy because of reduced capacity to metabolize certain drugs.

Neurodevelopment

The following 6 levels of behavioral state or the level of arousal (wakefulness) are recognized:

1. **Level 1:** Deep sleep
 2. **Level 2:** Sleep with rapid eye movements (REM)
 3. **Level 3:** Drowsy state (quiet wakefulness)
 4. **Level 4:** Quiet active, alert state; good interaction with environments
 5. **Level 5:** Awake and active state
 6. **Level 6:** State of active intense crying.
- Within the first hour or two after birth, the newborn spends a substantial time in level 4. In the subsequent few days, the infant spends just around 10% of the day in this state.
 - During the first week, the infant is capable of maintaining visual fixations on faces (human faces in particular), light, or movements against passive movements of his body, the so-called **doll's eye reflex**.
 - The orienting response refers to the spectrum of behavior of a newborn to environmental stimuli in the form of startle, altered heart rate, alertness and suppression of spontaneous movements. As a result of repetition of the stimulus, habituation of the response occurs and there is less startle and cardiac acceleration.
 - The neonatal behavioral assessment scale (NBAS) is designed to provide a far better assessment of the neonate's behavior than the conventional neurologic examination. In predicting future development and function, NBAS perhaps provides a more accurate prognosis during the first couple of weeks than the Apgar score at 1 and 5 minute. The scale determines the behavior in the following 4 dimensions:
 1. **Interactive processes**—orientation, alertness, consolability, cuddliness.
 2. **Motor processes**—muscular tone, motor maturity, defensive reactions, hand-to-mouth activity, general activity level and reflex behavior.

- 278 3. **Control of physiologic state**—habituation to a bright light, rattle and pinprick and self-quieting behavior.
4. **Response to stress**—tremulousness, lability of skin color and startle reaction.

Psychosocial Development

Experiences during pregnancy, labor and first hours after delivery have the effect of bonding the parents to some degree to the infant. This realization has led to revision in traditional practices, leading to involvement of parents in prenatal programs, encouragement of family-centered activities for pregnancy and childbirth, boosting of breastfeeding and rooming-in arrangements in the neonatal period.

PRIMITIVE NEONATAL REFLEXES

Among the large number of primitive neonatal reflexes, the following should be elicited for their normalcy, sluggishness or exaggeration and symmetry (Figs 17.24 to 17.32).

Moro Reflex

First described by Moro, an Austrian pediatrician towards the end of 19th century, it consists of rapid abduction (at shoulder) and extension (at elbows) as also complete



Fig. 17.24: Grasp reflex (Grade I).



Fig. 17.25: Grasp reflex (Grade III).



Fig. 17.26: Rooting reflex.



Fig. 17.27: Suckling reflex.



Fig. 17.28: **Stepping reflex:** Note that the neonate shows movements of walking when held upright and inclined forward with soles touching a flat surface. Placing reflex consists of flexion followed by extension when the dorsum is drawn along the under edge of a table.

opening of the hands followed by adduction and flexion of the arms or embrace equivalent.

This is best elicited by any of the following two maneuvers:

1. The baby is put supine on the cot or table. Then his hands are grasped and he is pulled so that the shoulders are



Fig. 17.29: Moro reflex (phase I): Sudden drop of the flexed head by 30 degree, results in rapid abduction and extension of upper limbs.



Fig. 17.31: Glabellar reflex: On tapping the nasion; the eyes close, "sunset" sign, lid lag and a characteristic grin.



Fig. 17.30: Moro reflex (phase II): The response in phase I is followed by adduction and reflexion of the arms.



Fig. 17.32: Extensor plantar (Babinski) response.

lifted a few cm, but the head remains in touch with the surface, causing an angulation between the head and the trunk. At this point, the hands are suddenly released to cause sudden extension of the neck.

2. The neonate is held supine over the hand and arm. Then, the flexed head is suddenly allowed to drop by around 30°.

Moro reflex is complete after 32 weeks of gestation though it may be elicitable in only 20–25% of the neonates. It can be elicited even after 28 weeks of gestation but the abduction component is rather weak. Abnormal Moro reflex occurs in the following situations:

- **Depressed/absent:** Cerebral depression, sedation, crying infant, hypertonia, hypotonia and shock.
- **Exaggerated:** Cerebral irritability.
- **Asymmetrical:** Fracture of clavicle or humerus, brachial palsy (Erbs palsy), spastic hemiplegic cerebral palsy (CP).
- **Downward rolling of eyeballs as in sunset sign, lid lag and a characteristic grin:** Kernicterus.
- **Persistence beyond 3 months:** Suspected CP.
- **Persistence beyond 9–12 months:** Pathognomonic of CP.

Startle Response

A sudden, sharp blow is given over the cot or table close to the neonate's head. A positive response consists of sudden

abduction (at shoulders) followed by adduction and flexion (slow) or embrace equivalent. Though Moro-like, 2 differences are conspicuous:

1. Elbow remains flexed and hands closed.
2. Outward and inward arm movements are less pronounced.

McCarthy Reflex

Tapping supratentorial area causes homolateral blinking. In abnormal neonates, elicitation of the reflex occurs even from tapping other areas over vertex.

Rooting and Suckling Reflexes

Stimulation of the lip or angle of the mouth, say with a fingertip or the breast nipple as such, causes the infant seek the stimulus (rooting reflex) and movements of the lips and tongue in the direction of the stimulus (suckling reflex). Suckling reflex can be further evaluated by introducing a finger into the infant's mouth and noting the strength as well as the rhythm of suckling. It is strong and well synchronized with swallowing at 32 weeks. At 28 weeks, it is weak and not synchronized with swallowing. In sick infants too, it is weak.

Glabellar Reflex/Tap

It comprises of tapping of the glabella or nasion (the meeting point of forehead and nose). The neonate reacts by closure of eyes or blinking.

280 Grasp Reflex

It consists of placing the examiner's index finger on the neonate's palm. The infant immediately grasps it. The grasp is so firm that he can be lifted off the cot by means of this only. On stroking the dorsum of the hand, he opens the fist, thereby releasing the examiner's finger.

A prototype of palmar grasp can be elicited by stroking the plantar surface of toes of the neonate. The infant responds by flexing the digits (plantar grasp). The grasp reflex is complete in a term neonate. By 34 weeks it is only partially present. Persistence of grasp reflex beyond 12 weeks of age points to brain damage.

Crossed Extension Reflex

Stroking the foot as the leg is held extended at knee causes flexion, abduction and extension, and adduction together with fanning of the toes of the other leg. The response simulates warding off painful stimuli. Incomplete and in a random purposeless manner, it is elicited at 32 weeks. At term, it is complete.

Tonic Neck Reflex

On suddenly turning a supine neonate's head to one side, the arm and leg of the same side extend and those of the other side get flexed. Persistence of the reflex beyond the age of 6–9 months, or maintenance of the tonic neck posture constantly even at an early age point to existence of CP.

Traction Reflex

This reflex is elicited by holding the supine neonate at the wrists and then pulling him up. The infant responds by flexing the arms and neck.

Plantar (Babinski) Reflex

It is elicited by stimulating the lateral aspect of the sole of the foot, beginning at the heel and extending to the base of the toes, with a firm object such as examiner's thumb or a handy key. The positive response is characterized by extension of the great toe and fanning of the other toes. Before showing characteristic extensor response, most neonates show an initial flexion of the great toe. Asymmetry of the Babinski reflex between extremities is a vital lateralizing sign.

Chvostek Sign

This well known sign of latent tetany may be present in normal neonates. It is elicited by tapping the area anterior to the external auditory meatus, thereby stimulating the facial nerve. The neonate responds by a twitch of the upper lip or the full mouth as a result of contraction of the orbicularis oris.

Two primitive reflexes (not neonatal) appearing at 8–9 months of intrauterine life are:

1. **Parachute reflex:** This reflex consists of suddenly lowering the neonate from a short distance in ventral

suspension. The maneuver is followed by extension of arms, hands and fingers.

2. **Landau reflex:** When the neonate is suspended in prone position with the examiner's hand under the abdomen, he responds by extension of head, trunk and hips. On flexing the head, trunk and hips also show flexion.

SOME MINOR PROBLEMS OF THE NEWBORN THAT MAY CAUSE PARENTAL ANXIETY

Physiological Jaundice

This benign condition is described under "Neonatal jaundice" in this very chapter.

Vomiting

Swallowed amniotic fluid may be responsible for some vomiting on the first day in most normal neonates. It needs no intervention. In case it persists, stomach wash should be done with normal saline and the infant is given only 5% glucose in water in place of the subsequent two feeds. Aero-phagy or erratic feeding may be responsible for regurgitation/vomiting. Proper burping usually solves the problem.

Transitional Stools

Within 12–24 hours, the infant passes dark meconium. In 2–3 days, stools change color to yellow-green and are loose and frequent. These are called **transitional stools** and are perfectly normal in infants fed on mother's milk.

Constipation

Whereas breastfeed infants may pass several motions, in bottle-feed babies, the usual complaint is constipation as a result of hard casein curds. Mothers must never be encouraged to give laxatives to such a baby.

Toxic Erythema (Erythema Toxicum)

In term infants, an erythematous rash (like a flea bite) may appear on the second day and disappear on its own by fourth day without any treatment. There are no systemic manifestations. The cause is unknown. No bacteria have been cultured from the lesions.

Milia

These are multiple yellow-white, 1 mm size, cysts which may be few or numerous. The sites are nose, nasolabial folds, cheeks and forehead. No treatment is needed since they disappear spontaneously in the first few weeks.

Mongolian Spots

These are blue-black macules usually found over the lumbosacral area, buttocks (Fig. 17.33) and, occasionally, back and shoulders in 70% of the Oriental newborns. The macule may be as big as 10 cm in diameter and even larger. The cause is infiltration of melanocytes in deep layer of dermis.



Fig. 17.33: Mongolian spots. Note the large blue-black macules. These spots tend to disappear as the infant grows, usually in the first few years. These are harmless.

Disappearance occurs gradually as the infant grows, usually during first few years. Traces may persist into adult life. The condition is harmless.

Salmon Patches (Macular Hemangioma, Nevus Simplex, Stork Bites)

Pinkish capillary hemangiomas may be present over nape, eyelids (upper) and glabella (Fig. 17.34) in 30–50% of normal newborns. Disappearance occurs in the first year though nuchal lesions may persist in one-fourth of the adult population.

Benign Neonatal Hemangiomatosis (BNH)

Multiple capillary hemangiomas, varying from pinhead to 20 mm in diameter, may be present only over the skin, right at birth or appear somewhat later. They show rapid increase in size till 2 weeks of age. Then, they begin to regress spontaneously. By fourth month, complete involution occurs. BNH needs to be differentiated from diffuse neonatal hemangiomatosis which also involves the viscera and may bleed profusely.

Harlequin Color Change

When the newborn is placed on his side, a sharp midline divides the body into a pale upper half and a very red lower half. The cause appears to be temporary imbalance in the autonomic regulatory mechanism of the cutaneous vessels. Such an episode has no pathologic significance.

Epstein Pearls

Lateral to the midline of the hard palate may be seen whitish spots, one on each side (Fig. 17.35). These are supposedly epithelial inclusion which is of no significance.

Sucking Callosities

These signify attempts of the baby at sucking during intra-uterine life. These are seen as button like cornified plaque over center of the upper lip.

Physiological Mastitis

Bilateral swelling of the breasts, which is hormonally induced, may occur about the third or fourth day and disappear



Fig. 17.34: Salmon patches.



Fig. 17.35: Epstein pearls. Note two white spots on hard palate, each lateral to the midline.

spontaneously by 2–3 weeks. No treatment is indicated. The common practice of massaging and expressing milk (the so-called *witch's milk*) is unfounded and may do harm rather than any good. The condition should, however, be differentiated from the infective mastitis or breast abscess which may result from infection with *Staphylococcus* or *Escherichia coli*. Breast abscess is usually unilateral.

Vaginal Bleeding

Withdrawal of maternal hormonal supply may cause slight vaginal bleeding on third day. It disappears by seventh day and is harmless.

Subconjunctival Hemorrhage

A neonate may show a subconjunctival hemorrhage close to the outer canthus. It subsides in a matter of few days without any intervention.

Natal (Congenital) Teeth

Rarely the newborn may be born with one or two already erupted teeth (Fig. 17.36). These need not be extracted unless they interfere with breastfeeding or they are loose. Julius Caesar had natal teeth.



Fig. 17.36: Natal teeth. Also termed congenital teeth, the condition is rare and harmless. Extraction is indicated if teeth are loose or if they interfere with feeding.

Cephalhematoma

Already dealt with under “Birth injuries” in this very chapter.

Caput Succedaneum

Already dealt with under “Birth injuries” in this very chapter.

Hiccup (Hiccough)

The term refers to sudden, involuntary, jerky diaphragmatic contractions, causing abrupt inspiratory episodes against a closed or closing glottis. It occurs intermittently after feeds in normal infants and is of no significance. If the attacks are prolonged, discomfort, fatigue and malnutrition may develop. The remedial measures include tickling the nostril, orbital pressure, carotid sinus pressure, induction of vomiting and therapy with drugs such as chlorpromazine or metoclopramide.

Nasolacrimal Duct Blockade

A proportion (2%) of the newborn may have persistent watery discharge and even conjunctivitis (usually unilateral). It is usually due to simple congenital obstruction of the nasolacrimal duct and clears spontaneously by 1–3 months. All that is needed is frequent wash of the eye with a moist sterile swab and gentle massage of the skin over the tear passage. In the presence of an infection, antimicrobial eye drops may be indicated. In case of blockade persisting in later months, surgical correction is necessary after the child has attained the age of 2 years.

Umbilical Hernia (Fig. 17.37)

It is a commonly encountered condition in newborns. The cause is weakness or faulty closure of the umbilical ring. It may be found in otherwise normal infants, but may well be a manifestation of cretinism or gargoylism in the presence



Fig. 17.37: Umbilical hernia. No intervention is needed. Most umbilical hernias resolve by end of first year without any treatment.

of some other manifestations of the disease. Two types are recognized—**false first**: False in which hernia occurs into the cord itself. It is persistence of the physiologic condition. **Secondly**, i.e. true, protrusion is through the umbilical cicatrix. It occurs in 25–50% of Oriental infants which is 6–10 times higher than the incidence in the whites. Normally, it has a tendency to reduce in size after 6 months (when the infant begins to sit and abdominal muscles develop) and subside by the age of 18 months spontaneously. The old practice of strapping it (with or without a large coin) may actually interfere with its spontaneous regression. Unlike paraumbilical or inguinal hernia, it seldom causes strangulation or incarceration.

Hydrocele

Noncommunicating hydrocele, more often on the right side, presenting with a well transilluminated scrotal swelling is quite common in neonates. It usually disappears spontaneously by 6 months of age. In case of its persistence beyond one year of age, herniotomy is needed.

Nonretractable Prepuce (Physiological Phimosi)

Many male newborns may have a prepuce that is adherent to the underlying glans. This is a physiological finding and disappears in due course. The condition should be considered pathological only if the difficulty in retracting the prepuce over the glans is persistent beyond 3 years of age and causes bulging of the foreskin on passing urine.

Mothers need to be advised not to attempt to forcibly retract the so-called **nonretractable foreskin**.

Hymenal Tags

About 60% of normal baby girls show mucosal tags at the margin of the hymen. These are of no particular significance.

THE PRETERM INFANT

By definition, the term refers to a baby born before a gestation period of 37 weeks (259 days).

- **Early preterm or extremely preterm:** When born before 28 weeks
- **Very preterm:** When born between 28+0/7 week and 33+6/7 weeks
- **Late preterm:** When born between 34+0/7 and 36+0/7 weeks

Preterm neonates contribute to a large chunk of LBW, i.e. weighing less than 2500 g. Such a baby measures 46 cm or less in length (crown-heel) and has head circumference of 32 cm or less. The chest circumference is usually less than 30 cm.

Predisposing Causes

- Poor nutritional status of the mother
- Maternal illness like toxemias, antepartum hemorrhage (APH), anemia and chronic infections
- Excessive smoking and drugs
- Overwork, fatigue and mental tension etc.
- Twinning
- Increasing parity
- High altitude.

Characteristic Features

The special features of the preterm infant are shown in Figure 17.38 and Box 17.10.

Though until recently believed to be entirely the result of supplemental oxygen, retinopathy of prematurity (ROP) is now hypothesized to have light as a significant contributory factor in its development. Bright light is supposed to act by producing chemically excited state and generating free radicals.

In short, a preterm baby has several disadvantages that predispose him to risks. The more the immaturity, the poorer are the chances of survival of such a baby.

CLASSIFICATION OF INTRAUTERINE GROWTH RETARDATION (IUGR)

- **Asymmetrical IUGR:** The baby appears marasmic, long and thin, skin losing its normal elasticity and hanging in

Box 17.10 Special feature of preterm neonates

- Relatively, and head is large
- Craniotables present
- Fine fuzzy and scanty hair
- Large fontanels and sutures
- Poor ear cartilage
- Absent eyebrows, but prominent eyes
- Buccal pad of fat is prominent
- Excessive lanugo hair present all over the body
- Small chest
- Breast nodules very small or absent with small nipple
- Relatively large abdomen
- Liver, spleen and kidneys are often palpable
- Umbilical hernia may be present
- Visible gut peristalsis may be there
- Undescended testes, light-coloured scrotal skin with few rugosities are seen
- In girl child labia majora does not cover labia minora (Fig. 17.39)
- On soles—very few creases are seen
- Nails are soft
- Overall poor musculature and less subcutaneous fat
- Higher frequency of apneic spells, aspiration, bradycardia, neurologic immaturity
- Anemia of prematurity
- Hypothermia
- Hypoglycemia
- Feeding difficulties
- Functional ileus
- Intraventricular hemorrhage
- Necrotizing enterocolitis
- Retinopathy of prematurity (earlier termed **retrolental fibroplasia**) (Fig. 17.40).
- Hemorrhagic disease of the newborn
- Rickets of prematurity.

folds over the buttocks. Internal organs with the exception of brain are shrunk. Since it occurs in third trimester, there is the so-called **brain-sparing effect**. Hence, the head circumference remains nearly normal and is over 3 cm more than the chest circumference. Ponderal index* is below 2 against the normal of over 2.5. Since

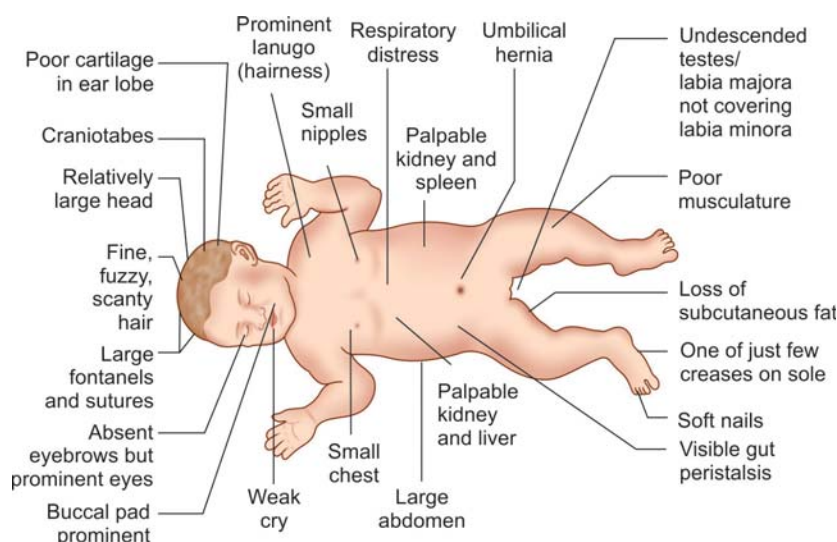


Fig. 17.38: Special features of a preterm baby.

* Ponderal index = Weight (g) × 100/Length (cm)³



Fig. 17.39: Prematurity. Note popliteal angle of 180°. Also note that labia minora and clitoris are edematous so that labia majora are widely placed and not covering labia minora.

cell number is not affected, these infants are responsive to nutritional rehabilitation. Maternal malnutrition, pregnancy-induced hypertension and other diseases and placental insufficiency are important in development of asymmetrical IUGR.

- **Symmetrical IUGR:** Such a baby is proportionately small in all parameters. Since cell population is reduced, growth potential is considerably affected, resulting in permanent retardation of physical and mental growth. Incidence of accompanying congenital malformations is high. Genetic and chromosomal disorders as well as intrauterine/congenital infections, TORCH/(S)yphilis, (T)oxoplasmosis, (O)ther agent, (R)ubella, (C)ytomegalovirus (STORCH) which cause early insult to the fetus are important in development of symmetrical IUGR.
- **Mixed IUGR:** Such a baby neither appears as malnourished as in asymmetrical IUGR nor as hypoplastic as in symmetrical IUGR. Reduction in both cell size as well as number is characteristic of this type of IUGR.

Etiology

- **Maternal malnutrition:** Food deprivation, particularly during the last weeks of pregnancy, more so when the mother is already undernourished (weight under 40 kg, height under 145 cm) leads to birth of malnourished infant. There is evidence that adequate food supplementation in pregnancy considerably reduces the incidence of IUGR.
- **Intrauterine infections:** Intrauterine infections such as toxoplasmosis, cytomegalovirus disease, rubella, herpes, syphilis, etc. may exert their adverse influence early in embryonic life causing hypoplastic type of IUGR.
- **Placental dysfunction:** Maternal problems such as toxemias of pregnancy and hypertension may be responsible for placental dysfunction and IUGR.

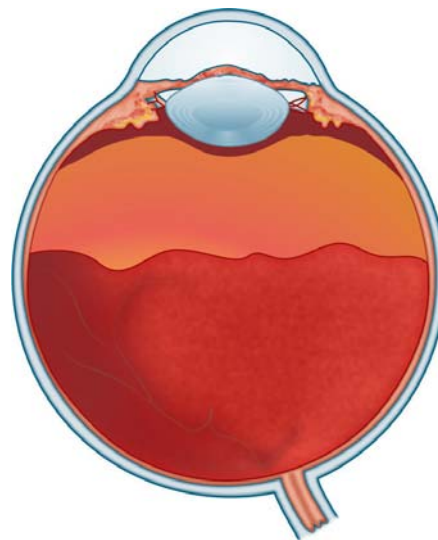


Fig. 17.40: Retinopathy of prematurity (ROP). An artist's depiction of the condition developing in a premature infant's eye as a result of blood vessels growing into the vitreous anteriorly.

- **Maternal diseases:** Chronic maternal diseases such as heart disease, tuberculosis, renal disease and bronchial asthma, etc. are likely to cause IUGR.
- **Genetic/chromosomal disorders:** Certain genetic disorders (short-limbed dwarfism) and chromosomal disorders (Turner syndrome, trisomies) exert their adverse influence early during gestation, reducing both cell number and cell size. The result is hypoplastic IUGR with reduced growth potentials.
- **Twin pregnancy:** After 35 weeks of gestation, the mother is not capable of providing adequate nourishment to more than one fetus.
- **Miscellaneous:** Teenage pregnancy, narcotic addiction, teratogenic agents, tobacco smoking, high altitude, irradiation and pregnancy-out-of-wedlock.

LOW BIRTH WEIGHT (LBW) INFANTS

- Depending on weight in relation to gestational age, neonates may be:
 - Appropriate for gestational dates (AGA)
 - Small for age dates (SFD)
 - Large for dates (LFD).
- **According to the World Health Organization (WHO):**
 - LBW babies refer to babies with a birth weight of 2,500 g or less
 - Very low birth weight (VLBW) refers to a birth weight between 1,000 g and 1,500 g
 - Extremely low birth weight (ELBW) refers to a birth weight less than 1,000 g
 - Micro premie is the term applied for babies below 500 g birth weight.

LBW may be due to prematurity, IUGR, or both. The magnitude of infants in developing world is enormous. Out of a total of 22 million such infants in the world, 21 million belong to the developing countries. India's share is quite substantial—7–10 million. LBW constitutes 30% of live births in India.

Handicaps/Risks of LBW

LBW from IUGR/SFD/SGA

- Aspiration of meconium, amniotic fluid or vernix caseosa
- Birth (perinatal) asphyxia as a result of cerebral anoxia
- Hypothermia
- Hypoglycemia
- Polycythemia from chronic hypoxia
- Food intolerance
- Permanent retardation in linear growth and psychomotor development.

LBW from Prematurity

- Birth asphyxia (perinatal)
- Hypoglycemia
- Hypocalcemia
- Hypothermia
- Respiratory distress syndrome (RDS)
- Pulmonary hemorrhage
- Lower respiratory tract infection (LRTI)—Pneumonia
- Sepsis
- Hyperbilirubinemia
- Anemia.

Management

The foremost job of the pediatrician is to identify if the LBW infant is sick or is stable. Management is dictated by this decision. The team should be prepared to prevent/tackle the risks/handicaps mentioned above as also complications.

- Arrangements should be in place for:
 - Resuscitating an asphyxiated infant
 - A baby with aspiration
 - A baby with congenital malformations
 - A baby with hemodynamic instability.
- Early feeding not only prevents hypoglycemia, but also leads to rapid weight gain after 3–4 days of age.
- Warm chain, including kangaroo mother care (KMC) and frequent monitoring for hypothermia.
- Infection control measures (hand hygiene, aseptic techniques, minimal handling and high index of suspicion).
- Handling of metabolic derangements.
- Handling of respiratory distress, including RDS.
- Handling of problems such as jaundice, polycythemia, anemia, IVH, ROP, etc.

Appropriate feeding is crucial for immediate survival, growth and development and long-term neurodevelopment in LBW infants. Details of feeding of LBW infants are given elsewhere in this Chapter.

Prognosis

Intrauterine growth retardation infants are easy to feed and show rapid weight gain after age of 3–4 days, which slows down after the age of 6 months. Though prognosis is much better than in preterm infants, mortality is 2–3 times higher than in normal babies.

Whereas permanent retardation in physical growth is a feature of hypoplastic babies, the malnourished infants, particularly those with hypoglycemia, show higher incidence of brain damage (learning disability, metabolic bone disease {MBD}) and suboptimal physical growth later in life.

Prevention

- **Female literacy and formal education:** A well-informed, educated mother is likely to have better health before and during pregnancy, avoid harmful agents and influences during pregnancy and show better reproductive performance and outcome. Education and training of the traditional birth attendants (TBAs) to ensure adequate care of the mothers during pregnancy and their referral to a nearby health center in case of high-risk pregnancy is also important.
- **Maternal health status:** Adequate nutrition of the female throughout childhood and adolescence is a very effective way of ensuring good health status of pregnant women, provided that the so-called **previous nutritional status** is maintained by continued good nourishment and freedom from medical ailments.
- **Antenatal care:** There is evidence that birth weight is directly proportional to the number of antenatal check-ups. Early detection of high-risk factors such as intrauterine infections, hypertension, toxemias of pregnancy and early intervention can prevent occurrence of IUGR.
- **Maternal infections:** Malaria, urinary tract infection (UTI), TORCH/STORCH, etc. if prevented or if tackled in time, can considerably reduce the incidence of IUGR.

ESSENTIAL NEWBORN CARE

Basic Principles

- To ensure adequate oxygenation through clear airways and proper breathing.
- To prevent hypothermia in the neonates.
- To encourage early and exclusive breastfeeding for healthy neonates or suitable method of providing nutrition to weak and sick babies who cannot feed on breast and get adequate nutrition.
- Suitable measures to prevent neonatal infections.
- Early identification of at risk newborn, offer suitable initial management and stabilization of the baby; if possible or arrange for safe transfer to suitable advanced neonatal care center.

Immediate Care at the Time of Delivery

- Clean and safe delivery by properly TBAs including doctors, nurses or other category of health workers in a well-equipped institution.
- Prompt and systematic resuscitation whenever indicated.
- Adoption of minimum five cleans during every delivery (Box 17.11).
- Maintenance of warm chain or measures to prevent hypothermia.

Box 17.11 Five cleans during delivery

1. **Clean surface:** Clean sterile sheet and towel
2. **Clean hands:** Hand hygiene, using sterile gloves
3. **Clean cord tie:** Clean and sterile ties/clamp
4. **Clean cord blade:** Clean and sterile blade/scissor for cutting the cord.
5. **Clean cord:** Dry cord with no application whatsoever.

- Promotion of early and exclusive breastfeeding preferably within half-one hour of birth for every normal newborn.

Care in First Few Hours

- Warm chain
- Exclusive breastfeeding, initiated within half-one hour of birth, with counseling and support from the health provider
- Vitamin K1, 0.5–1 mg, IM
- Measures to prevent neonatal infections
- Management of common problems of neonates
- Early detection of high-risk cases and management
- Safe and suitable referral to special care/intensive care centers.

Care Beyond First Few Hours

- Exclusive breastfeeding.
- Appropriate immunizations—Bacillus of Calmette Guerin (BCG), Hepatitis B and oral polio vaccine (OPV) zero dose.
- Care of cord—dry, clean cord; no application.
- Interaction with mother on:
 - Motivational activities favoring breastfeeding and other matters concerning baby's welfare.
 - **Sleeping position for baby:** Current recommendation is supine position rather than prone position.
 - **Rooming-in (bedding-in):** Mother should be encouraged to indulge in rooming-in, i.e. keeping the baby with her in the same bed.
 - **Bath:** It is advisable to postpone the formal bath to the beginning of second week. By this time the umbilical stump is shed and the local area becomes clean. This cuts down risk of local infection. However, sponging may be given after 24 hour of birth.
 - **Oil massage:** If the family insists on oil massage, it may be allowed provided that it is done very gently, hygienically and using only safe oil such as coconut oil. Irritant oils like mustard oil should not be employed.
 - **Harmful practices:** Harmful practices such as instilling kajal or surma in eyes, prelacteal feeds, application of something on the cord, withcraft, etc. must be discouraged.

Discharge and Follow-up

All normal newborns need to stay in the hospital for a minimum of 24 hours; others longer depending on the

Box 17.12 Essential criteria that should be satisfied before the newborn is discharged

- Detailed examination done and recorded.
- Breastfeeding is established. Adequacy is indicated by the infant passing urine 6–8 times/24 hours and sleeping well for 2–3 hours after each feed.
- Requisite immunization for the period already given.
- There is no medical problem except for physiological jaundice.
- Mother has been adequately counseled, has developed confidence for giving proper care at home and has understood to look for **red-flag signs** – danger signals (feeding difficulty, hypothermia with temperature less than 35.5°C or fever with temperature more than 37.5°C, seizures, lethargy) for which the baby needs to be brought back to the facility.
- Health education to mothers—proper mother care techniques like feeding, bathing, infection and prevention measures, etc.
- Proper discharge slip has been prepared and handed over to parents.
- Regular growth monitoring.
- Developmental assessment and further follow-up, if required.

merits of the situation. Before discharge, certain criteria must be met (Box 17.12).

Follow-up

First follow-up visit—normal at 6 weeks when check-up as well as immunization can be given. For high-risk (preterm, LBW, exaggerated/pathological jaundice) neonates follow-up is within 2–3 days of discharge. At every stage, local traditional practices involving neonatal health should be studied in detail and then encourage the useful ones and stop the harmful ones.

DETERMINATION OF GESTATIONAL AGE AT BIRTH

It is important to differentiate between the preterm and the IUGR babies. This has a bearing on management, including that of complications and the prognosis. Since the dates of last menstruation are frequently not forthcoming from the illiterate mothers, assessment of gestational age may be made on the basis of physical and neuromuscular criteria. Box 17.13 presents the physical signs suggesting a gestational age of less than 37 weeks. Yet another method of determining the gestational age is fetal ultrasonographic evaluation.

The expanded new Ballard scoring system (that includes the extremely premature infants) employing detailed physical and neuromuscular criteria for maturity is recommended for this purpose (Tables 17.3, 17.4 and Fig. 17.41).

Box 17.13 Physical signs suggesting a gestational age of less than 37 weeks

- **Genitalia**
 - **Male:** Small scrotum with few rugosities, testes at external inguinal ring
 - **Female:** Widely separated labia majora with exposed labia minora and clitoris
- **Breast nodule:** Less than 5 mm diameter
- **Ear cartilage:** Deficient with poor elastic recoil
- **Scalp hair:** Woolly (fine) or fuzzy (fluffy).

Table 17.3: Expanded new Ballard scoring system: Physical criteria for maturity

	-1	0	1	2	3	4	5
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash, few veins	Cracking, pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40–50 mm: -1 <40 mm: -2	<50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases on ant. 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola—no bud	Stripped areola, 1-2 mm bud	Raised areola, 3-4 mm bud	Full areola, 5-10 mm bud	
Eye/ear	Lids fused loosely (-1), tightly (-2)	Lids open, pinna flat, stays folded	Slightly curved pinna; soft; slow recoil	Well-curved pinna, soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals, male	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals, female	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Table 17.4: Expanded new Ballard scoring system: Calculation of maturity rating from physical and neuromuscular scores

Score	-10	-5	0	5	10	15	20	25	30	35	40	45	50
Weeks	20	22	24	26	28	30	32	34	36	38	40	45	50

	-1	0	1	2	3	4	5
Posture							
Square Window (Wrist)	>90°	90°	60°	45°	30°	0°	
Arm Recoil		180°	140°-180°	110°-140°	90°-110°	<90°	
Popliteal Angle	180°	160°	140°	120°	100°	90°	<90°
Scarf Sign							
Heel to Ear							

Fig. 17.41: Expanded new Ballard scoring system. Neuromuscular criteria for maturity.

DANGER SIGNS IN A NEWBORN

(Red Flag Signs)

A healthy neonate is warm to touch, has pink palms and soles and feeds well. The signs listed in Box 17.14 point to existence of an illness. Presence of one or more of these signs is an indication for prompt evaluation.

NEONATAL THERMAL DISORDERS

The newborn is known for instability of thermal (heat regulating) mechanism with a tendency to land up in hypothermia and infrequently, in hyperthermia.

As a rule, his ideal body temperature (axillary) should be 36.5–37.5°C. In hypothermia, it is less than 36.5°C and

Box 17.14 Danger signs warranting monitoring**General**

- Off color and lethargy
- Poor feeding
- Cold skin (hypothermia)
- Fever
- Poor weight gain/excessive weight loss (>15%) in first week
- Bleeding

Pulmonary

- Tachypnea (respiratory rate >60/min)
- Chest retractions/indrawing
- Apnea/grunting

Gastrointestinal

- True diarrhea
- Persistent vomiting
- Distention of abdomen
- Failure to pass meconium within 24 hours

Neurological

Seizures

Genitourinary

Failure to pass urine by 48 hours

Skin

- Umbilical sepsis
- Pyoderma
- Sclerema.

in hyperthermia more than 37.5°C. Clinically, a reasonable idea about newborn's body temperature may be made by the rapid, but crude touch method. The examiner (doctor, nurse or health worker) touches the infant's hands, feet and abdomen by the back of hand.

If abdomen is warm but hands and feet are cold, it is considered **cold**—a warning sign for cold injury. In case all three, i.e. abdomen, hands and feet are cold, hypothermia is the assessment. The standard method of measuring newborn's body temperature is axillary thermometer. Continuous monitoring of newborn's body temperature, usually in an incubator and radiant warmer is skin probe. Warm chain, comprising of 10 steps (Box 17.15), is a strategy aimed at maintaining ideal body temperature. In the hospital settings, incubators and radiant warmers are employed to maintain normal body temperature of sick and preterm/small neonates.

NEONATAL HYPOTHERMIA**(Cold Injury)****Definition**

Neonatal hypothermia is defined as axillary temperature less than 36.5°C. It is further categorized as:

- **Cold stress:** 36–36.5°C
- **Moderate hypothermia:** 32–36°C
- **Severe hypothermia:** Less than 32°C.

Etiology

The newborn, a preterm infant in particular, is highly susceptible to exposure to low environmental temperature. This can happen in situations such as:

Box 17.15 10 steps of warm chain

1. Warm labor/delivery room with a minimal temperature of 25°C
2. Warm resuscitation
3. Immediate drying
4. Skin to skin contact—keeping the neonate on mother's abdomen, KMC
5. Breastfeeding—frequent and exclusive
6. Delayed bathing—best postponed to end of first week by which time the cord has fallen
7. Appropriate clothing; wrapping in several layers of warm, but light clothes rather than a single layer of thick cloth
8. Rooming in/co-bedding
9. Professional alertness—well-trained and sensitized healthcare providers
10. Warm transportation.

Abbreviation: KMC, kangaroo mother care.

- Winter months
- Sudden change in weather conditions
- Resuscitation procedure
- Cold snap.

Clinical Features

- Low body temperature (35–30°C or even less), cold skin with or without acrocyanosis (from peripheral vasoconstriction).
- Further drop in temperature, say around 25°C, may cause sclerema (i.e. solidification of the subcutaneous tissue with the result that the skin feels hard and fixed to the underlying structures).
- Lethargy, refusal to accept feed and bradycardia with pulse less than 60/minutes (from {central nervous system} CNS depression).
- Hypoglycemia, hypoxia and metabolic acidosis (from high metabolism).
- Tachypnea and respiratory distress (from high pulmonary artery pressure).
- Disseminated intravascular coagulation (DIC) may occur, leading to hemorrhagic manifestations including massive, pulmonary hemorrhage.
- Sepsis may further complicate the picture.

Treatment

- **Mild-moderate hypothermia (32–36.5°C):** Immediate rewarming by skin to skin contact on a warm bed room in a warm room; may use radiant warmer, convection-warmed incubator.
- **Severe hypothermia (less than 32°C)**
 - Rewarming the infant using suitable facility (air-heated incubator, radiant warmer, thermostatically-controlled heated mattress)
 - Slowly giving 10–20 mL of 25% glucose IV
 - Maintenance of electrolyte balance
 - Oxygen
 - Steroid therapy in case of sclerema
 - Vitamin K in case of bleeding
 - Exchange transfusion if DIC is the likely cause of hemorrhages
 - Antibiotics.

Prognosis

Mortality is in the range of 25–50%. Survivors show high incidence of brain damage.

Prevention

(Measures for Warming the Baby)

Box 17.15 lists the ten steps of keeping the neonate warm.

SCLEREMA

Definition

The term is applied to solidification of the subcutaneous fat.

Etiopathology

Sclerema should arouse suspicion of:

- Cold injury
- Gram-negative septicemia
- Hypernatremic dehydration.

Irrespective of the underlying cause, the neonate is in a moribund state. Histologic changes include broadening of the trabecular fat and diminution in fat spaces. There is no cellular infiltration.

Clinical Features

The overlying skin becomes hard and stretched and cannot be pinched. The condition first makes its appearance over the face and the legs. Thereafter, it spreads in a centripetal fashion. With the involvement of the thorax, respiratory difficulty (shallow and rapid breathing) and cyanosis may occur.

Treatment

Therapy is directed at the underlying cause together with high doses of steroids.

Prognosis

Prognosis is usually grave. Recovery occurs, despite aggressive treatment, only in a small proportion of cases.

KANGAROO MOTHER CARE (KMC)

Definition

Kangaroo Mother Care is a very effective method of providing nursing and warmth through skin to skin contact to preterms/LBW infants, especially in resource-limited countries (as a substitute for the expensive incubator) (Fig. 17.42). KMC was first launched by Prof. Edgar Rey Sanabria and Prof Martinez of the University of Colombia, Bagota, Latin America in 1979 in response to shortage of incubators and severe hospital infections.

Benefits

- Maintenance of infant's temperature
- Promotion of exclusive breastfeeding
- Promotes extrauterine adaptation
- Builds up mother's confidence



Fig. 17.42: Kangaroo mother care (KMC). Note that the baby is held upright against the mother's skin and between the breasts and covered with mother's clothes plus an additional shawl/blanket. A belt around mother's waist may assist in keeping the baby in position.

- Better growth
- Protection against infection
- Reduction in frequency of apneic spells
- Better mother-infant bonding.

Prerequisites

- **Neonate-related**
 - The neonates should have no medical problem.
 - He should be hemodynamically stable.
 - He should be able to breastfeed, at least partially.
- **Mother-centric**
 - The mother should be healthy, willing and cooperative.
 - She should maintain good hygiene.
 - She should maintain good dietary and supplement intake.

Method of Administration

- Essentially, the naked baby is placed between mother's breasts in an upright position for skin to skin contact for many days at a stretch.
- Appropriate clothing is employed to hold the baby in position.
- During sleep, the mother maintains a semi-recumbent posture at an angle of 60 degree so that the baby remains upright. This assists in keeping the baby warm all times.
- He is made to feed at the breast on demand (minimal 2 hourly).
- In between, when she has to take bath or take rest, father or some other family member may do kangarooing. Else, the baby may be wrapped in woolen clothing.
- KMC should be continued even after the discharge from the hospital until the baby has reached 2.5 kg weight and a gestation of 37 weeks.

290 Termination of Administration

Kangaroo mother care may be withdrawn in the following circumstances:

- Baby has reached a weight of 2.5 kg and gestation age of 37 weeks.
- Baby has become quite active. This is indicated by the following actions when the baby is offered KMC:
 - Crying
 - Pulling extremities out
 - Attempt to wriggle out.

INCUBATOR CARE

A modern incubator, available in most specialized nurseries, is an excellent device to maintain temperature and humidity according to baby's requirements.

- The recommended nursery temperature is around 30°C. The incubator temperature should be such as will maintain the axillary temperature of the baby between 35–37°C as clarified in Table 17.5.
- A low reading rectal thermometer, graduated for 20–40° range, is a must for accurate recording of the baby's temperature.
- A humidity of 60–70% suffices under most circumstances.
- Lastly, an incubator infant should be left unclothed. This enables accurate observations of his general condition, color, respiration, etc. Further, such a baby should not be given bath.

Whereas an incubator is an excellent device for thermoregulation of extremely low birth weight (ELBW) and gravely sick neonates, its disadvantages include difficult access to the baby, difficulty in carrying out prolonged procedures such as exchange transfusion, high-risk of infection and high cost.

RADIANT WARMER (OPEN CARE SYSTEM)

This is an economic alternative for the expensive incubator for providing microenvironment for high-risk neonates. Though it is not preferred for ELBW and gravely sick neonates, its positive points include:

- Easy access to the baby
- Less risk of nosocomial infection
- Most appropriate for doing prolonged procedures like exchange transfusion or surgery and
- Affordable cost.

NEONATAL HYPERTHERMIA

In tropical climates, infants with inadequate fluid intake and infants exposed to high environmental temperature which may be in natural sun, in an incubator, in a photo-

therapy unit or in a bassinet close to a room heater or radiator, may occasionally develop on second or third day hyperthermia with a body temperature of 38–39°C.

Clinical Features

Manifestations in these infants include restlessness, irritability, weight loss, diminished frequency and output of voiding, loss of skin elasticity, depressed anterior fontanel and thirst. Infrequently, tachycardia and tachypnea develop. In contrast to the sick looking neonate when infection is the cause of high temperature, in this condition, also termed **dehydration fever** or **transitory fever of the newborn**, he shows vigor, taking fluid avidly.

A severe form of hyperthermia develops in neonates and infants who are warmly dressed for the low outdoor temperature and left close to a heater in a room or made to travel in a warm vehicle. The poor sweating capacity of the neonate contributes to development of fever with a temperature as high as 41–44°C.

Manifestations include flushing, apathy, dry and warm skin. Later, stupor, grayish pallor, coma, seizures and hemorrhagic shock may follow. Sudden death may occur at usual room temperature or immersion in tepid water.

Treatment

Fluid and electrolyte imbalance, if present, should also be corrected. Response to rehydration or lowering of environmental temperature is excellent.

Prevention

Prevention consists of dressing the infant in clothing appropriate for the temperature of the immediate environment.

BREASTFEEDING

Once oxygenation and temperature is maintained, breastfeeding should be started within half to one hour. It is best suited for a newborn. It is not only species specific, but also baby specific. It contains all the nutrients for normal growth and development of a baby from the time of birth to first six months of life.

Composition

- **Energy:** 67 Kcal/dL
- **Protein:** 0.9–1.3 gm/dL
- **Fat:** 3.8–4.5gm/dL
- **Carbohydrate:** 6.8 gm/dL.

Benefits

- Adequate calories, easily digestible and bioavailable proteins and adequate amount of necessary fat.
- 88% of water with low osmolarity, thus decreasing the solute load on kidney.
- Prevents against infection.
- Helps in mental development and enhance bonding.

Breastfeeding should be initiated as soon as possible after birth (within ½ to 1 hour after vaginal delivery and 2–4 hours after cesarean section). Colostrum should not be

Table 17.5: Incubator temperature setting

Weight of the baby	Recommended temperature
Below 1,000 g	35–36°C
1,000–1,500 g	32–35°C
1,500–2,000 g	30–32°C

thrown away. Exclusive breastfeeding should be continued till 6 months of age. No gripe water, no multivitamin drop should be given and complement food should be started after six months of exclusive breastfeeding. Breastfeeding can be continued till child reaches two years of age. If the baby is not able to take direct breastfeeding than expressed breast milk (EBM) can be given through katori spoon (KS) or nasogastric tube.

Reflexes with Breastfeeding

- **Rooting reflex:** It helps baby to find the nipple and proper attachment to breast.
- **Suckling reflex:** It helps the baby draw out milk from mother's breast. It consists of:
 - Drawing in the nipple and areola to form an elongated teat inside the mouth.
 - Pressing the stretched nipple and areola with jaw and tongue against the palate.
 - Drawing milk from lactiferous sinuses by wave like peristaltic movement of the tongue.
 - Swallowing reflex.

Technique of Breastfeeding

- **Position:** Comfortable position for mother and her baby either sitting or lying down. Baby's head and neck should be supported in a straight line with his body and should face the breast. Baby's cheek should touch the mother's breast.
- **Latching:** It means attachment of nipple along with areola in baby's mouth and not nipple alone. Good attachment at breast is a key to successful breastfeeding. To suckle effectively, a baby should be well latched on the breast and should be able to take nipple and enough areola into the mouth for effective sucking.
- **Burping:** The baby should be put on left shoulder, the head has to be supported with mother's left hand and then with the right arm support the buttocks and gently pat on the baby's back with right hand. Is a must after feeding the baby to avoid regurgitation.
- **Adequacy of breastfeeding:** If the mother is confident, baby is passing urine 6–7 times a day, passing well-formed stools, sleeping comfortably after feed for at least 2–3 hours at a stretch, gaining weight adequately.

Ten Steps of Successful Breastfeeding

1. Have a written breastfeeding policy that is routinely communicated to all health care staff.
2. Train all health care staff in skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within half-hour of birth.
5. Show mothers how to breastfeed and how to maintain lactation even if they should be separated from their infants.
6. Give newborn no food or drink other than breast milk, unless medically indicated.

7. Practice rooming-in—allow mothers and infants to remain together 24 hours a day.
8. Encourage breastfeeding on demand.
9. Give no artificial teats or pacifiers (also called **dummies or soothers**) to breastfeeding infants.
10. Foster the establishment of breastfeeding support groups and refer mothers to them on discharge from the hospital or clinic.

FEEDING THE LBW INFANT

Feeding Problems of the LBW Infant

The LBW infant, known for immaturity of the gastrointestinal system, frequently suffers from one or the other feeding problem:

- Excessive crying because of the need for a higher food intake compared to the normal infant in order to make up the deficit in weight.
- High frequency of suckling difficulties.
- Incoordination between suckling and swallowing.
- Abdominal distention as he is not capable of holding a large feed in his stomach.
- Regurgitation since the cardioesophageal sphincter is lax.
- Poor tolerance for saturated fatty acids.

Notably, most of the problems are secondary to immaturity of the gastrointestinal system.

Nutritional Needs of the LBW Infant

According to estimates, the LBW infant requires on an average 140 (120–150) kcal/kg/day. Understandably, about 200 mL of milk is required to meet this demand. Attempts to attain this target right at the outset often prove futile since the infant is simply unable to cope with this much feed. A realistic and practical approach is to aim at achieving this target by second week.

As regards protein, 4–6 g/kg/day is good enough. An intake outside this range is not in the interest of the infant. Higher intake may cause retention of fluid and solute, as also high blood urea on account of renal immaturity. Rapid weight gain occurring in this situation is not in the interest of the baby. Low protein intake may cause hypoproteinemic edema and poor weight gain, further worsening the baby's nutritional status.

Over and above this, the infant also needs vitamin K at birth and multivitamins (especially vitamins A, C, D and E), iron and folic acid, calcium and phosphorus, etc. subsequently. **Early feeding** is the current recommendation—within 6–12 hours. Most centers give the first feed at about three hours of age. The risk of aspiration in early feeding can be minimized with careful supervision and vigilance. **Risks of delayed feeding** include icterus, hypoglycemia, metabolic acidosis, metabolic acidosis and brain damage.

Method of Feeding/Providing Nutrition

Broad guidelines for fluids and nutrition of LBW infants are discussed above.

292 **Breastfeeding**

Many LBW infants, especially those weighing more than 1800 g are strong enough to suckle well from the breast. This should be encouraged. However, care should be exercised to safeguard against distention of abdomen. This is best achieved through small feeds at frequent intervals.

Breastfeeding should be considered as the preferred choice for enteral feeding for all LBW babies. When it is not workable for some reason, gavage feeding (tube feeding) should be the choice, employing mother's own expressed milk. There is sufficient evidence that necrotizing enterocolitis (NEC) is far less in LBW infants fed one mother's milk than in those on artificial feed. Further, LBW infants on own mother's milk are known to grow faster than those on another woman's milk.

Alternative Methods of Milk Feeding

- **Gavage (Tube) feeding** is needed in:
 - LBW infants weighing less than 1200 g or less than 30 weeks gestation after initial stabilization with IV fluids.
 - LBW infants weighing 1200–1800 g or less than 34 weeks gestation.
- Other indications of tube feeding are:
 - Baby getting tired quickly.
 - Baby taking more than 20 minutes to finish the feed.

For LBW infants, recommended size of the tube is **no. 6 FG** (French gauge) and **no. 4 FG** in case of complicating respiratory difficulty. On an average, about 16–17 cm of tube is needed to reach the stomach from the gum margin. In a given situation, the tube may be measured from the tip of the nose to the ear lobe and further to the ansiform cartilage. The measurement should be marked of the tube per se. In case tube feeding is required for a short period, it may be passed through the mouth. For this purpose, the wet tube is placed along the side of the tongue and then into the pharynx. The head end of the baby needs to be raised.

If tube feeding is needed for several days, it should be passed through the nasal route into the esophagus and stomach. It should be kept in place. Once the tube has been passed—irrespective of the route—its position should be confirmed. To do this, gentle aspiration is required. The gastric fluid is usually colorless and acidic in reaction. If aspiration is difficult, some air may be injected and its entry into the stomach verified by auscultating the epigastric region.

Intermittent Feeding

The outer end of the tube is attached to a syringe (20 mL) containing milk. It is important to bear in mind that milk should not be pushed, if safety is needed. Instead it should be allowed to trickle by gravity. The time taken by each feed nearly varies from 10–20 minutes, depending upon the size of the feed. This is about the time taken by an ordinary feed as well.

At the end of the feed, a few mL of plain water should be pushed to rinse the tube. If the tube is to be removed, it should be pinched so that no fluid trickles into the trachea as the end reaches past the larynx.

Continuous Feeding (Intragastric Drip)

Continuous milk drip has now won pride of the place in the feeding of LBW babies. Its advantages are many, e.g:

- Allows high milk intake
- Weight gain is more
- Less risk of regurgitation
- Less risk of aspiration into the lungs
- Less risk of hypoglycemia
- Nursing time is cut
- Minimal handling of the infant.

The technique of introduction of the tube into the stomach is same as in case of intermittent feeding. The outer end of tube is, however, attached to the intravenous set containing milk. As in intermittent feeding, infant's head should remain slightly raised. His position should be supine. The tube should be changed every third day. It should be aspirated thrice daily. The bottle requires to be changed every 12 hours and the giving set every 24 hours.

Palady/Katori-spoon Feeding

The fact that even LBW neonates of 30–32 weeks gestation are good at swallowing even though their sucking may not be upto the mark forms the guiding principle of feeding by a **palady** or **katori and spoon (KS)**.

In case of the palady, the tapering snout is placed at the angle of the mouth. Then, milk is allowed to trickle slowly. The infant manages to swallow it without sucking. Repeat until the required quantity has been fed. It is good to be slow and patient, to avoid spilling of the feed.

In case of KS, required quantity of EBM is taken in a clean medium-sized katori (or a cup). Spoon is filled with milk and placed over the lips at the corner of the mouth. Milk starts flowing into the mouth while the infant actively swallows it. Repeat the process until the calculated quantity has been fed. Avoid spillage. It is possible to find the quantity that has been spilled by weighing the napkin around baby's neck before and after the feeding.

Expressed Breast Milk

Expressed breast milk should be the first choice. Milk for the LBW baby should provide higher protein and calories. It is, therefore, not only species-specific, but also baby specific on account of its best suitability for the infant. Expression of milk can be carried out by mother's attendant though mother herself is the best for this purpose. The choice about the manual expression or the use of a breast pump is influenced by the existing circumstances as well as mother's attitude. Box 17.16 gives the schedule for expression of breast milk.

Expression of milk must be done in a safe and clean manner. The concept of human milk banking, now gaining popularity in the European countries poses several

Box 17.16 Breast milk expression

- **First 24 hours:** Twice, 2 minute at each breast
- **Second 24 hours:** Thrice, 3 minute at each breast
- **Third 24 hours:** Four times, 4 minute at each breast
- **Fourth day and onward:** Five or 6 times, 5–10 times at each breast.

difficulties in the developing countries, because of unfavorable climate, ignorance, illiteracy and impracticability of monitoring of each sample before administration and holder pasteurization. Nevertheless, in view of the greater need for human milk for the LBW infants, the need for modified human milk banking cannot be denied.

Expressed milk provides adequate amount of protein, energy, vitamins and copper and nearly adequate amounts of zinc, iron and magnesium which, however, are needed in yet greater measure by the LBW baby. It is poor in calcium and phosphorus. Supplementation with these nutrients is therefore important in the care and feeding of LBW infants.

In case enough EBM from the biologic mother is not readily available, it may be collected from another lactating healthy mother. Resort to top milk is indicated only in case of lactation failure despite best of efforts at relactation. It should be for a short period only and breastfeeding resumed as soon as possible.

Nutritional Supplements

Preterm human milk, though superior to pooled term milk, is deficient in iron, calcium, phosphorus, zinc and copper. It provides more proteins and energy but the preterm LBW infant needs yet more of these. EBM, therefore, works better when supplemented with human milk fortifier or individual nutrients.

- **Human milk fortifiers (HMF):** At present, the only available HMF in India is Lactodex-HMF (Raptakos-Brett). At two weeks of age, human milk fortifier may be added to EBM for providing extra protein, energy and micronutrients. The dose is 2 g of Lactodex-HMF for 50 mL of EBM. The resultant fortified EBM provides additional 0.2 g protein, 0.19 g, fat, 1.2 g carbohydrate plus calcium, phosphorus, vitamins, minerals and trace elements.
- **Vitamins and micronutrients:** Vitamin, micronutrient and mineral supplementation is recommended as per Box 17.17.

Intravenous (Central) Feeding

- **Initially:** It may be needed in certain situations.
- **First two Days:** For LBW of SGA (SFD) type, 90–100 mL/kg of 5–10 % glucose is recommended. For LBW of short gestation type, 60–70 mL/kg of 5–10 % glucose suffices.
- **Later:** Since the LBW needs extra sodium and potassium, N/5 saline with 15% potassium chloride (1 mL added to 100 mL infusate) should replace the 5–10% glucose after 2 days. The readymade isolyte-P serves well as an alternative.

Parenteral Nutrition

It may become mandatory to resort to parenteral nutrition in the following life-threatening situations in which enteral

Box 17.17 Vitamin, micronutrient and mineral supplementation in LBW infants

- **Infants weighing 1500–2500 g**
 - **Vitamin K:** Right at birth, 1 mg vitamin K should be given IM.
 - **Vitamin D:** At 2 weeks, 400 IU × 1 year of age.
 - **Iron:** At about 4–8 weeks, low-dose (2mg/kg/day) iron supplementation should be started × 1 year of age.
- **Infants weighing less than 1500 g**
 - **Vitamin K:** Right at birth, 1 mg vitamin K should be given IM.
 - **Multivitamin drops:** At 2 weeks, multivitamin (including folic acid) drops × 40 weeks of age.
 - **Vitamin D:** At 2 weeks, 400 IU × 1 year of age.
 - **Iron:** At about 4–8 weeks, low-dose (2mg/kg/day) iron supplementation should be started × 1 year of age.
 - **Vitamin E, calcium and phosphorus:** Supplementation with these micronutrients is recommended, especially in case of VLBW × 40 week age.

Abbreviations: IU, international unit; VLBW, very low birth weight; LBW, low birth weight; IM, intramuscularly.

feeding has failed to establish or central feeding is not possible for prolonged periods:

- ELBW babies (less than 1000 g)
- LBW babies unlikely to attain full enteral nutrition by day five for some associated problem such as intractable diarrhea, NEC, surgically correctable gastrointestinal (GI) anomaly (omphalocele, gastroschisis, tracheoesophageal fistula, malrotation with volvulus and diaphragmatic hernia, etc.) and extensive bowel resection.

This regimen provides adequate fluids and electrolytes, energy (from glucose, protein and lipids), amino acids and vitamins and micronutrients for sustained growth of the LBW babies. With this method, providing around 100 kcal/kg/24 hours, a weight gain of 15 g/kg/24 hours is likely to be attained in the first week.

Parenteral nutrition may be carried out employing an indwelling central venous catheter (per cutaneous or surgically-placed) or through a peripheral vein. It is important to be vigilant about the complications, both catheter-related and metabolic (Table 17.6).

Table 17.6: Complications of parenteral nutrition and remedial measures

Complication	Action recommended
Catheter-related complications, sepsis/septicemia (usually from coagulase negative staphylococcus)	<ul style="list-style-type: none"> • Meticulous catheter care <ul style="list-style-type: none"> ■ Aseptic preparation of the infusate • Appropriate antibiotics • Removal of line if sepsis persists
<ul style="list-style-type: none"> • Thrombosis • Extravasation of fluid • Accidental dislodgement of catheter • Metabolic complications • Hyperglycemia • Azotemia • Nephrocalcinosis • Hyperlipidemia • Hypoxemia • Hyperammonemia • Cholestatic jaundice • Liver disease • Metabolic bone disease 	Biochemical and physiologic monitoring.

294 Non-nutritive Suckling

When the LBW infant is being kept on IV fluid or tube feeding, he may be given experience of suckling by providing opportunity to suckle the empty breast. This experience stands him in good stead later at the time of transition to nutritive suckling.

This is a method of exposing a neonate, who is being kept on gavage feeding or intravenous fluids/nutrition for reasons such as prematurity, LBW or illnesses such as birth asphyxia, septicemia, etc. to experience of suckling on emptied breast that is expected to stand him in good stead later at the time of transition to nutritive suckling.

Characteristics

Non-nutritive suckling consists of a rhythmic alternation of bursts of rest periods with a mean intersuckling interval of 0.3–0.5 second. Nutritive suckling, on the other hand, consists of almost continuous streams of suckles with a mean intersuckling interval of 0.1 second.

Advantages

Non-nutritive suckling influences the neonatal behavior of a preterm baby in the following ways:

- Restless state is less frequent.
- Behavior distress during a painful procedure is altered.
- Oxygenation, weight gain and gut transit time are increased.
- Nutrient absorption is improved. Intermittent changes in pressure during suckling are necessary to stimulate secretion of the lingual lipase, facilitating fat absorption.
- Transition from gavage to breast becomes easier.
- Nipple stimulation by repeated suckling results in enhanced milk supply. An added advantage of non-nutritive suckling is that it provides significant emotional support and satisfaction to the mother who is upset by the high-risk status of the infant.

Procedure

Make sure that the procedure is carried out in a reasonably warm room to safeguard against chilling of the infant. Then, mother is asked to express out milk from each breast as much as possible. After this, the baby is allowed to suckle on each breast. The requisite amount of the expressed milk is administered by tube feeding. Gradually, the infant should be suckling on the emptied breast before each and every gavage feed.

As soon as the infant develops well sustained suckling, start direct breastfeeding. Slowly withdraw all gavage feed and let the infant be entirely on direct breastfeeding.

HYPOXIC-ISCHEMIC ENCEPHALOPATHY (HIE)

(Birth Asphyxia Perinatal Asphyxia)

Definition

The term, *hypoxia*, means inadequate arterial oxygen concentration. The term, *ischemia*, denotes inadequate blood flow to cells or organs so that their normal function-

Box 17.18 Causes of hypoxic-ischemic encephalopathy

Fetal hypoxia

- Hypoventilation during anesthesia, cardiac failure or carbon monoxide poisoning leading to inadequate oxygenation of maternal blood.
- Spinal anesthesia or compression of vena cava and aorta by gravid uterus leading to maternal hypotension.
- Uterine tetany from excessive use of oxytocin leading to poor relaxation of the uterus and poor placenta filling.
- Premature separation of placenta.
- Compression or knotting of the umbilical cord, leading to impedance to the circulation of blood through the cord.
- Cocaine causing uterine vessel vasoconstriction.
- Toxemias and postmaturity leading to placental insufficiency.

Postnatal hypoxia

- Anemia from severe bleeding or hemolytic disease.
- Shock from adrenal hemorrhage, IVH, fulminant infection or massive blood loss.
- Poor arterial oxygen saturation from cerebral defects, necrosis or injury.
- Poor oxygenation of blood from cyanotic CHD or deficient pulmonary function.

Abbreviations: IVH, intraventricular hemorrhage; CHD, congenital heart disease.

ing suffers. The resultant encephalopathy is an important cause of neonatal death, CP and/or mental retardation.

Etiopathogenesis

Two major groups are recognized—(1) fetal hypoxia and (2) postnatal hypoxia (Box 17.18).

The fundamental insult, perinatal hypoxia and birth asphyxia, initiates a spectrum of neuronal biochemical alterations and alterations in cerebral perfusion, leading to selective necrosis of the neurons of deeper cerebral cortical layers with the resultant various neurologic manifestations of HIE. A notable feature is that whereas in fullterm babies major area of involvement is parasagittal cerebral, in case of preterm babies it is deeper periventricular white matter. Nonbrain involvement includes damage to:

- Cardiovascular system (CVS) (heart failure, myocardial ischemia)
- Kidneys (acute tubular necrosis {syndrome of anti-diuretic hormone} SIADH)
- GI tract (NEC)
- Blood (DIC)
- Liver
- Lungs (reduced surfactant, persistent pulmonary hypertension, pulmonary edema, pulmonary hemorrhage).

Clinical Features

- Before delivery, manifestations include IUGR, slowing of fetal heart rate with variable or late deceleration pattern and acidosis in scalp blood analysis. To safeguard against fetal death or CNS damage to the infant, mother must be administered high concentration of oxygen and the delivery conducted immediately.
- At delivery, meconium staining of the amniotic fluid indicates fetal distress. Manifestations in these infants

Box 17.19 Sarnat and Sarnat staging of hypoxic-ischemic encephalopathy			
Signs	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic	Stuporous, coma
Muscle tone	Normal	Hypotonic	Flaccid
Posture	Normal	Flexion	Decerebrate
Tendon reflex	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriasis	Miosis	Unequal, poor light reflex
Seizures	None	Common	Decerebration
EEG	Normal	Low voltage changing to seizure activity	Early periodic pattern, later totally isopotential
Duration	Less than 24 hr	2–14 days	Days–week
Outcome	Good	Variable	Death, severe deficits

Abbreviation: EEG, electroencephalogram.

include failure to breathe spontaneously, hypotonia, change from hypotonia to hypertonia, pallor, cyanosis, slow heart rate, unresponsiveness to external stimuli, seizures, congestive cardiac failure (CCF), cardiogenic shock, respiratory distress syndrome, persistent pulmonary hypertension, GI perforation, hematuria and acute tubular or cortical necrosis.

- After delivery, hypoxia is characterized by dyspnea and cyanosis, in particular, appearing within minutes of birth and is secondary to respiratory failure and circulatory insufficiency.

Box 17.19 gives the time-honored Sarnat and Sarnat staging system for HIE. This staging plus magnetic resonance imaging (MRI) findings provide information about the prognosis for the HIE infant. Mild HIE usually has a normal outcome. In severe HIE, mortality is 75%; and as high as 80% of survivors develop neurologic sequelae. A neonate who receives significant resuscitation at birth and who goes on to show signs of encephalopathy should be assessed by Sarnat Staging between 24 and 48 hours after birth.

The standard (original) Sarnat and Sarnat staging combines clinical and electroencephalogram (EEG) findings. The system is called the **modified Sarnat staging** when only clinical findings (without EEG) are taken into consideration.

Differential Diagnosis

A large number of conditions fall in the differential diagnosis of HIE. These include hypoglycemia, sepsis, severe hyperbilirubinemia, intracranial hemorrhage (ICH), idiopathic cerebral infarction, congenital neuromuscular diseases, congenital dysmorphic syndromes and inborn errors of metabolism.

Diagnosis

Clues in the history and a thorough neurologic examination may be supported by EEG, visual-evoked responses (VER), brainstem auditory-evoked responses (BAER), cranial sonography, computed tomography (CT) scan, MRI, nuclear magnetic resonance spectroscopy (MRS), near infrared spectroscopy (NIRS), single photon emission computed tomography (SPECT), positional emission tomography scan (PET) and intracranial pressure measurements.

Treatment

It consists of restricting fluids to 2/3rd of the total maintenance requirement, correction of hypoglycemia (maintaining blood glucose at 75–100 mg/dL), hypocalcemia and acidosis, control of seizures and provision of hyperventilation with 100% oxygen in order to maintain PaO₂ at 100–200 torr. In addition, the infant must be kept warm and his blood pressure maintained. Potassium needs to be avoided during first 24 hours.

New therapeutic modalities include:

- Prevention of free radical formation (allopurinol and its active metabolites)
- Free radical elimination (antioxidant enzymes, antioxidant free scavengers such as vitamin E)
- Excitatory amino acid antagonists
- Calcium channel blockers (flunarizine, nimodine)
- Substrate availability (glucose supplementation)
- Hypothermia (induced by cooling the head employing ice helmet).

Prevention

Careful monitoring of the fetus during labor and prompt and appropriate intervention at the earliest sign of fetal distress constitutes the hallmark of prevention of HIE.

Prognosis

Untreated severe HIE proves fatal in almost 30% of the cases. The following features are accompanied by bad prognosis:

- Severe encephalopathy characterized by flaccid coma, apnea, absent oculocephalic reflexes, refractory seizures and significant reduction in cortical attenuation on CT scan.
- Prematurity.
- Inability to control metabolic and cardiopulmonary complications like hypoxia, hypoglycemia and shock, etc.
- A low Apgar score at 20 minutes.
- Absence of spontaneous respiration and persistence of abnormal neurologic signs at 2 weeks of age.

Long-term Sequelae

These include impaired attention span, hyperactivity, mental retardation, CP (spastic diplegia or quadriplegia, choreoathetosis, ataxia), bulbar and pseudobulbar palsies, auditory deficits and seizures.

Definition

A neonate is said to be suffering from respiratory distress when he has tachypnea with a respiratory rate of 60/minute or more when quiet and when he has an inspiratory chest (intercostal) retractions and/or expiratory grunt, with or without cyanosis.

Assessment

In each and every infant with respiratory distress, it becomes mandatory to assess the gravity of the situation and to determine the factor(s) underlying the problem. Only then, one can initiate right type of management.

Two scoring systems are available:

1. **Downe's scoring system** for assessing the severity of the respiratory distress in term infants (Table 17.7).
2. **Silverman-Andersen (or simply Silverman) scoring system** for preterm neonates. It consists of five items (Table 17.8).

Each of the five factors is graded 0, 1, or 2. The sum of these factors yields the score. Adequate ventilation is indicated by a 0 and severe respiratory distress by a score of 10.

Etiology

As is evident from an appraisal of Table 17.9, a large number of conditions can cause respiratory distress in a newborn.

Table 17.7: Downe's scoring system for respiratory distress in term neonates

Features	Score 0	Score 1	Score 2
Respiratory rate	<60	60–80	80 or apnea
Cyanosis	None in room air	In 40% oxygen	In more than 40% oxygen
Retraction	None	Mild	Moderate or severe
Grunting	None	Audible with stethoscope	Audible without stethoscope
Air entry	Clear	Decreased	Barely audible

Note: Score Action needed
 0–4 Less than 40% oxygen
 5–7 Continuous positive airway pressure (CPAP)
 Over 8 Assisted ventilation in view of impending respiratory failure

Table 17.8: Silverman scoring system for respiratory distress in preterm neonates

Feature	Score 0	Score 1	Score 2
Chest movement	Equal	Respiratory lag	See-saw respiration
Intercostal retractions	None	Minimal	Marked
Xiphoid retractions	None	Minimal	Marked
Nasal flaring	None	Minimal	Marked
Expiratory grunt	None	Audible with stethoscope	Audible without stethoscope

Table 17.9: Causes of neonatal respiratory distress

Maternal	Toxemia, severe anemia, cardiovascular disease, abnormal uterine contractions, anesthesia or drugs
Obstructive	Aspirated material, macroglossia, glossoptosis, choanal atresia, vascular rings pressing on trachea, goiter, diaphragmatic hernia and tracheoesophageal fistula
Pulmonary	Respiratory distress syndrome, pneumonia, pneumothorax, pneumomediastinum, pulmonary edema or hemorrhage, pleural effusion, atelectasis, Wilson-Mikity syndrome*, bronchopulmonary dysplasia* and wet lung syndrome**
Neurologic	Central depression due to birth trauma, anesthesia, drugs, intracranial hemorrhage, phrenic nerve paralysis, intercostal muscle paralysis as in congenital poliomyelitis, Werdnig-Hoffmann disease, myasthenia gravis
Cardiac	Heart failure
Metabolic	Acidosis, alkalosis and organic acidemia

* These two conditions occurring in small for date (SFD), appear to result from oxygen toxicity. The prognosis is poor. Many of the affected infants die from a progressive respiratory illness like cor pulmonale or congenital cardiac failure (CCF).

** This almost benign condition is characterized by perihilar congestion and clears on its own in 2–4 days. Poor lymphatic clearing of alveoli appears to be the cause. The other name given to this condition is transient tachypnea of the newborn.

Diagnostic Approach

It is based on good history, clinical examination and investigations. Algorithm gives diagnostic approach to etiology based on gestation and age of onset (Fig. 17.43).

Management

Figure 17.44 gives an algorithmic approach to broad management of neonatal respiratory distress.

RESPIRATORY DISTRESS SYNDROME

(Respiratory Distress Syndrome {RDS} Type I, Hyaline Membrane Disease {HMD})

RDS or HMD is the topmost cause of neonatal respiratory distress in the West. In India, incidence appears to be relatively less (~1%) among live births, rising to about 8% among preterm (less than 32 weeks) infants. In infants less than 28 weeks gestation, incidence may be as high as 75–80%.

Etiopathogenesis

Exact etiology is not known. Reduction or absence of a substance, **surfactant**, that normally covers the surface epithelium of the air passages is said to be the fundamental lesion (Table 17.10). As a result, alveolar collapse and lack of adequate expansion occur. Pulmonary capillaries secrete fibrin that gets precipitated to form eosinophilic hyaline membranes over the bronchioles and alveoli. These membranes make the exchange of gases in the lungs difficult.

The earlier impression that aspiration of amniotic fluid plays a significant role in causation of HMD is now found

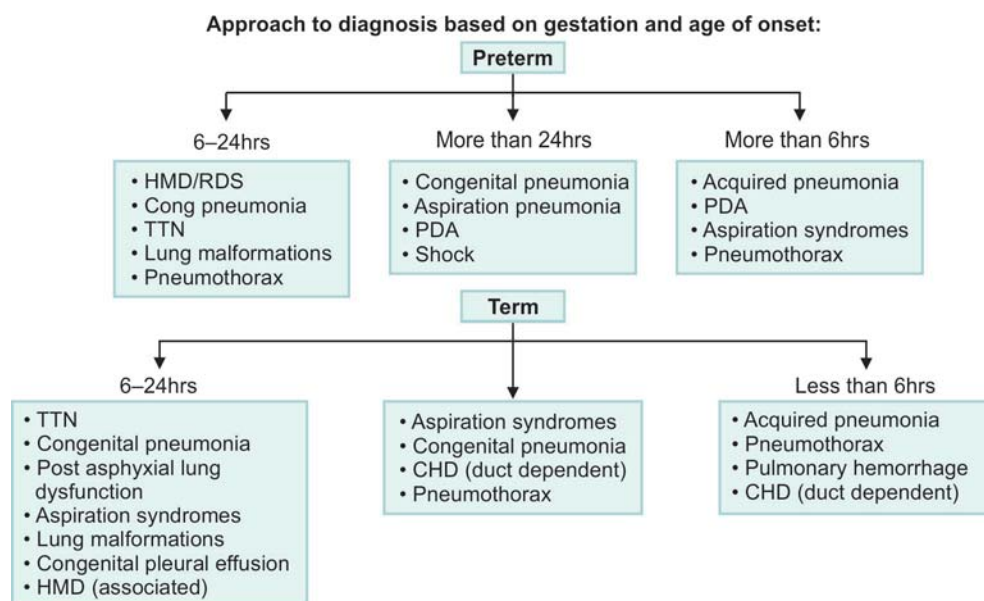


Fig. 17.43: Neonatal respiratory distress. Algorithmic approach to diagnosis based on gestation and age of onset.

Abbreviations: HMD, hyaline membrane disease; RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn; PDA, patent ductus arteriosus; CHD, congenital heart disease.

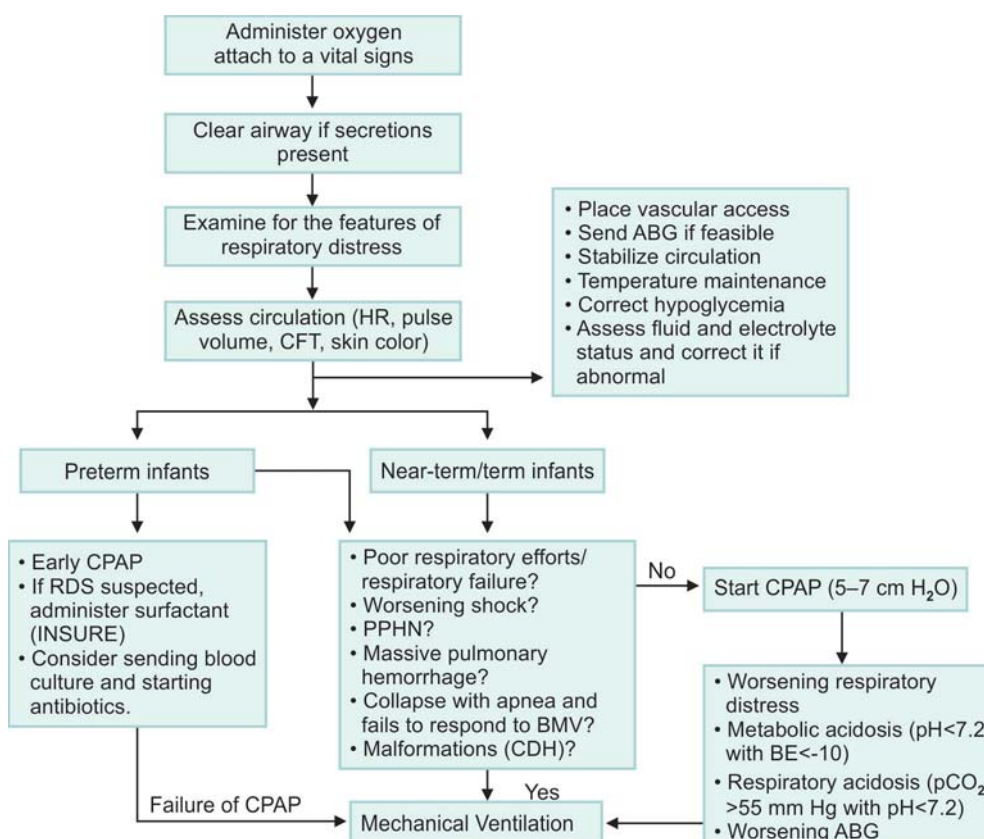


Fig. 17.44: Neonatal respiratory distress. Algorithmic approach to broad management of neonatal respiratory distress.

Abbreviations: HR, heart rate; CFT, capillary filling time; CDH, congenital diaphragmatic hernia; BMV, balloon mitral valvotomy; RDS, respiratory distress syndrome; CPAP, continuous positive airway pressure; ABG, arterial blood gases; PPHN, persistent pulmonary hypertension of newborn.

to be erroneous. HMD is principally a disease of preterm babies, born to diabetic mothers, after cesarean section, or following intrauterine respiratory distress. It is never seen in fullterm babies even though they may be SFD.

Clinical Features

The disease usually manifests right at birth (in some cases symptoms may be delayed for a few hours, often 6 hours) with progressively increasing respiratory distress.

Table 17.10: Salient features of commonly used surfactant preparations

Product (Company)	Source	Available volume	Concentration	Dose
Survanta (Abbot)	Bovine minced	8 mL and 4 mL	1 mL = 25 mg	<ul style="list-style-type: none"> • 100 mg/kg = 4 mL/kg • Maximum 2 doses at 6 hour gap
Curosurf (Nicholas)	Porcine minced	1.5 mL	1 mL = 80 mg	<ul style="list-style-type: none"> • First: 200 mg/kg = 2.5 mL/kg • Repeat: 100 mg/kg = 1.25 mL/kg • Maximum 2 doses at 12 hour gap
Neosurf (Cipla)	Bovine lavage	5 mL and 3 mL	1 mL = 27 mg	<ul style="list-style-type: none"> • 135 mg/kg = 5 mL/kg • Maximum 2 doses at 12 hour gap

Grunting respiration, flaring of alae nasi, retraction of ribs and sternum and cyanosis are usually prominent. Low blood pressure, hypothermia, hemorrhagic manifestations (DIC, pulmonary hemorrhage, IVH), hypoglycemia, gross metabolic disturbances, heart failure, pneumothorax, respiratory infection, etc. may complicate the clinical picture. Auscultatory findings are poor air entry and widespread crepitations over both lungs.

Diagnosis

Chest X-ray reveals ground-glass appearance and prominence of bronchial air shadows, the so-called **air bronchogram** pattern, extending beyond the left border of the heart. An X-ray taken at a later stage may show absolutely opaque lung field, the so-called **white-out lungs** (Fig. 17.45). Generalized, but patchy atelectasis occurs little later.

A negative gastric aspirate shake test, provided that the gastric aspirate is not contaminated with blood or meconium, supports the diagnosis. Definitive diagnosis is only possible at autopsy which shows, among other findings, lungs with liver-like consistency and a hyaline membrane uniformly lining the respiratory bronchioles.

Prevention

Respiratory distress syndrome can be suspected intranally in susceptible situations (maternal diabetes) by the following tests:

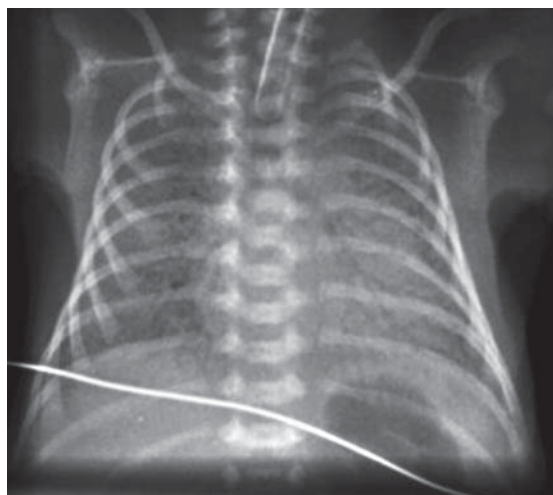


Fig. 17.45: Severe respiratory distress syndrome. Note the “white out” lungs, air-bronchogram and homogenous opacification of lungs obscuring the heart borders.

- Lecithin/sphingomyelin ratio in the amniotic fluid under 1.5 (a ratio exceeding 2 signifies maturity of the lung).
 - Amniotic fluid shake test/density by spectrophotometry, if negative.
 - Phosphatidyl glycerol, if absent. This is the most specific and most reliable test for testing the lung maturity and, thus, diagnosing HMD during intrauterine life.
- All possible efforts must, therefore, be made by the obstetricians to avoid premature labor so that gestational and pulmonary maturity is attained. Other measures, especially in unavoidable premature induction of labor and diabetic mothers with risk of premature delivery include:
- Administration of steroids (dexamethasone or betamethasone) 48–72 hour before delivery in case of fetuses of 32 week or less gestation, especially if lecithin in amniotic fluid indicates immaturity of the fetal lungs.
 - Administration of one dose of surfactant into trachea of premature neonates during 24 hours after birth. It reduces mortality from HMD.

Differential Diagnosis

A large number of conditions (Table 17.9) need to be considered in the differential diagnosis of RDS. Of special interest is the early-onset group B streptococcal infection (the late-onset group B streptococcal infection causes meningitis). Important differentiating points are:

- The disease is manifested with dyspnea, apnea and shock, nearly always before the infant is 3 hours old. HMD manifests during the first 6 hours.
- Prolonged rupture of membranes (PROM) and maternal febrile illness are usually present whereas these are unusual for HMD.
- Course of disease is short and fulminant whereas it is variable in HMD.
- Chest X-ray may show in addition to the findings seen in HMD, lower lobe opacities and exaggerated interstitial markings.
- Gastric aspirate cytology shows polyp and streptococci. In HMD, it is negative.

Treatment

The patient should be treated in a humidified incubator. Oxygen flow should be so regulated as to maintain the arterial oxygen concentration between 70–90 mmHg. The oxygen should be cut down as soon as possible to

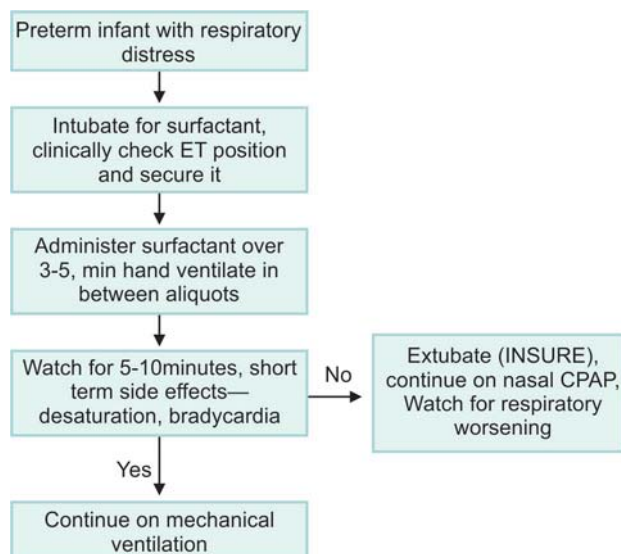


Fig. 17.46: Algorithm for administering surfactant.

Abbreviations: ET, endotracheal tube; CPAP, continuous positive airway pressure.

minimize the danger of retrolental fibroplasia and/or bronchopulmonary dysplasia. Humidity should be 60–80% in the incubator. The rectal temperature needs to be kept around 36.5°C. If the baby continues to be bad, CPAP by a respirator, a mask or intranasal tube should be given. CPAP avoids need for assisted ventilation in quite a proportion of infants with RDS.

If, despite 100% oxygen or CPAP, the infant shows poor response, assisted ventilation may be resorted to by an expert. The use of IV fluids, especially 1–2% sodium bicarbonate in 5–10% dextrose in water, to counter acidosis is of value. Its dose is 3–5 mEq/kg in 24 hours. It is better if the dose of sodium bicarbonate can be monitored by the pH of the arterial blood. For instance, the dose for a pH of less than 7.00 is 7 mEq/kg whereas for a pH of 7.25–7.30 it is only 1 mEq/kg.

Broad spectrum antibiotic cover (say ampicillin/cefotaxime plus gentamicin) should be given for underlying/superadded infection. Indomethacin, 0.2 mg/kg (0, IV) may be given 12 hourly for a total of 3 doses for the associated patent ductus arteriosus (PDA) which can worsen existing hypoxemia. Exogenous surfactant, instilled endotracheally, yields gratifying results (Table 17.10). Natural surfactants (derived from animal source, say calf are superior because of their surfactant-associated protein content. Therapeutic indication for surfactant is VLBW infants needing 30% oxygen and mechanical ventilation (rescue therapy) (Fig. 17.46).

The so-called *insure* approach involves intubation, surfactant and rapid extubation to CPAP. Exchange transfusion has a debatable role in the management of HMD.

Prevention

- Avoidance of premature deliveries and thereby prevention of pulmonary immaturity.
- Antenatal steroid (betamethasone, dexamethasone or glucocorticoid) therapy to all mothers in preterm (<35

week) labor. Over and above RDS, it reduces incidence of IVH, NEC, PDA, hemodynamic instability and overall neonatal mortality.

- Surfactant (endotracheal) first dose to symptomatic premature infants soon after birth or during the first few hours of life (early rescue).

Complications

These may well be secondary to prematurity or in relation to management.

- **Pulmonary:** Pulmonary interstitial emphysema, pneumothorax, pulmonary hemorrhage, bronchopulmonary dysplasia, leak syndromes and superadded sepsis/pneumonia and subglottic stenosis.
- **Extrapulmonary:** PDA, IVH, ROP.

Prognosis

Without treatment, RDS carries a bad prognosis. With appropriate and timely treatment, most infants (80–90%) can be saved. If the baby tides over first 2–5 days, natural remission (heralded by spontaneous diuresis) may occur. The survivors may suffer from neurologic, pulmonary or ophthalmic sequelae.

MECONIUM ASPIRATION SYNDROME

About 13% of all deliveries have meconium staining of amniotic fluid (MSAF). Around 6% of such neonates aspirate meconium into the lungs in utero, during delivery or immediately after birth and develop respiratory distress. This is termed *meconium aspiration syndrome (MAS)*.

Pathophysiology

Once there is aspiration of meconium, it may:

- Block the airway (both small and large). This causes patches of atelectasis and emphysema leading to pneumothorax and other air leak syndromes.
- Induce chemical pneumonitis.

The net result is ventilation perfusion mismatch ending up as respiratory failure.

Clinical Features

The most common presentation is a postmature and SFD infant with staining of nails, skin and umbilical cord with meconium and neurological and respiratory depression followed by varying degree of respiratory distress developing in first few hours of birth and persisting for several weeks. Left untreated, respiratory distress may worsen, ending up as respiratory failure.

Complications

- Airleak syndromes—pneumothorax, interstitial emphysema, pneumomediastinum, pneumopericardium, pneumoperitoneum, subcutaneous emphysema.
- Persistent pulmonary hypertension of the newborn, a major complication, is the most frequent cause of mortality.
- HIE.
- Pulmonary/cerebral hemorrhage.

- 300** ■ Superadded bacterial sepsis.
- Subglottic stenosis (due to prolonged endotracheal intubation).

Diagnosis

Diagnosis is primarily clinical (MSAF plus respiratory distress without an obvious cause) supported by chest radiography.

Chest X-ray shows overinflated lungs (areas of hyper-expansion) and segmental atelectasis, heterogeneous opacities, flat diaphragm, retrosternal lucency, bilateral pneumonia and signs of airleak syndromes. Cardiomegaly may also be present.

Arterial blood gases, complete blood count (CBC) and blood culture are needed.

Differential Diagnosis

This includes persistent pulmonary hypertension of the newborn, transient tachypnea of the newborn, spontaneous pneumothorax, lung malformations and cardiac disease.

Treatment

Meconium aspiration syndrome with mild respiratory distress show encouraging response to IV infusion and oxygen. MAS with severe respiratory distress needs ventilatory support (including high frequency ventilation as a rescue therapy). Role of steroids, antibiotics and surfactant therapy is controversial. In selected situations, extracorporeal membrane oxygenation (ECMO) is life-saving.

Prevention

Reduction in postmaturity is the most important route to reduction in incidence of MAS. All infants with evidence of MSAF should have oropharyngeal suction before delivery of shoulder and endotracheal suction under laryngoscopic visualization after delivery (but before he takes his first breath) in order to safeguard against meconium aspiration into the lungs.

Prognosis

Mortality as such is very high in severe MAS. However, it can be cut down to 30–40% with ventilatory support.

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN)

The term refers to severe respiratory distress as a result of persistent elevation in pulmonary resistance due to failure of normal circulatory transition at birth.

Etiology

Normally, circulatory transition at birth, in which pulmonary vascular resistance (PVR) falls drastically and systemic vascular resistance (SVR) increases, triggers closure of ductus arteriosus and foramen ovale. In PPHN, the PVR remains high and SVR low. The result is right to left shunt across the foramen ovale, or PDA manifesting as persis-

tent central cyanosis. PPHN is more frequently seen in term and post-term neonates. Asphyxia, MAS, RDS, CDH, PPH etc are its common causes.

Clinical Features

Severe respiratory distress with cyanosis as the presenting manifestation.

Diagnosis

Echocardiography assists in differentiating it from cyanotic congenital heart disease.

Treatment

Treatment is in the form of ventilatory support and medication with vasodilators such as nitric oxide, tolazoline, magnesium sulfate, adenosine, nitroglycerine, calcium channel blockers and bicarbonate and inotropes.

Prognosis

Prognosis is unfavorable.

TRANSIENT TACHYPNEA OF THE NEWBORN (TTN)

(Respiratory Distress Syndrome Type II, Wet-lung Disease, Neonatal Retained Fluid Syndrome)

The term refers to a benign self-limiting condition presenting soon after birth.

Etiology

It is secondary to delayed clearance of fetal lung fluid, occurring usually in fullterm neonates. Frequency is higher in neonates who are delivered by cesarean section. Quite a few factors may contribute to development of TTN (Box 17.20). As a consequence, alveoli are full of retained fluid which tends to inhibit gas exchange.

Clinical Features

Manifestations developing within a couple of hours after birth include

- Tachypnea or minimal respiratory distress (usual presentation)
- Mild grunting and nasal flaring
- Cyanosis and tachycardia
- Barrel-shaped chest
- Auscultatory findings in the form of crepitations.

Box 17.20

Contributing factor in the development of transient tachypnea of the newborn

- Relative surfactant deficiency
- Low adrenaline levels
- Lack of catecholamine surge during labor
- Delay on the part of fetal lung to switch over to fluid absorption from fluid secretion
- Maternal asthma causing predisposition to beta-adrenergic hyporesponsiveness.

Diagnosis

Chest X-ray shows hyperexpanded lung fields, prominent vascular markings, prominent interlobar fissure (because of fluid in them) and prominent perihilar streaking. Small pleural effusions and mild cardiomegaly may also be seen.

Differential Diagnosis

- Pneumonia
- Air-leak syndromes
- RDS
- Metabolic abnormalities
- Cardiovascular abnormalities
- CNS disorders.

Treatment

It is in the form of only symptomatic measures such as:

- Monitoring of heart rate, respiratory rate, oxygen saturation and blood pressure
- Maintenance of oxygen saturation between 94–100%
- Keeping the infant warm.

Prognosis

Outcome is excellent with wait and watch approach plus symptomatic measures. As the retained fluid is absorbed by the lymphatics, respiration shows improvement. Within 24–72 hrs, recovery is usually complete. The probability of subsequent development of asthma in infants with TTN should be borne mind.

BRONCHOPULMONARY DYSPLASIA (BPD)

(Chronic Lung Disease)

The term denotes damage to neonate's alveolar cells, interstitium and blood vessels as a result of barotrauma and oxygen toxicity.

Pathophysiology

Consequent upon insult to neonate's lung tissue from barotrauma and oxygen toxicity, there is release of inflammatory mediators. This is followed by increased permeability, resulting in leakage of water and protein and, later, fibrosis and cellular hyperplasias. Respiratory distress follows severe damage to lung.

Clinical Features

Manifestations include tachypnea and respiratory distress.

Diagnosis

Bronchopulmonary dysplasia is a clinical diagnosis in a preterm infant who received ventilator support and supplemental oxygen in first week of life or longer followed by bouts of sepsis and inadequate nutritional intake.

Differential Diagnosis

It includes congenital heart disease, interstitial pneumonia, recurrent aspiration, recurrent pneumonias, surfactant protein deficiency, pulmonary lymphangiectasia and Wilson-Mikity syndrome.

Treatment

Oxygen supplementation, glucocorticoids, diuretics, beta-agonists and anti-cholinergic agents along with good nutrition form the sheet-anchor of BPD treatment. Special immunization includes respiratory syncytial virus (RSV) and influenza vaccines.

Complications

- **Cardiac:** Pulmonary hypertension, cor pulmonale
- **Nutritional:** Failure to thrive as a result of chronic hypoxia, gastroesophageal reflex (GER), recurrent aspirations or heart disease
- **Diuretic-related:** Dyselectrolytemia, osteopenias
- **Steroid-related:** Neurologic sequelae
- **Beta agonist-related:** Enhanced large airway instability in infants with tracheomalacia and bronchomalacia.

Prognosis

These infants continue to have hospitalization and re-hospitalization for oxygen therapy of ventilator support on account of worsening BPD, reactive airway disease and pneumonia or RSV infection.

Subglottic stenosis, airway granulomas and pseudopolyps tend to persist in adolescence, warranting surgical intervention. Global neurodevelopmental impairment is common.

NEONATAL PNEUMONIA

A manifestation of sepsis, neonatal pneumonia is a common cause of respiratory distress in a newborn.

Etiology

Common etiologic pathogens are *E. coli*, *Staphylococcus aureus*, *Klebsiella pneumonia* and, in the West, group B *Streptococcus pneumonia* (GBS) though viruses, fungi and aspiration may also cause it.

Clinical Features

Manifestations include respiratory distress on top of other features of sepsis such as feeding difficulty, poor activity and hypothermia, etc.

Diagnosis

Diagnosis is by and large clinical supported with:

- Chest X-ray
- Complete blood count (CBC)
- Blood culture.

Treatment

Antimicrobials to cover both Gram-positive and Gram-negative pathogens, e.g. ampicillin/cloxacillin plus gentamicin/amikacin. For nosocomial infections—cephalosporins plus amikacin

Prognosis

Usually gratifying with timely instituted proper therapy.

302 PNEUMOTHORAX

Among airleak syndromes in neonates on ventilation (especially for MAS), pneumothorax (air in pleural cavity) is the most important and common cause of neonatal respiratory distress.

Diagnosis is clinical with assistance from transillumination of chest. Treatment is by needle aspiration. Alternatively, chest tube drainage may prove life-saving.

RECURRENT NEONATAL APNEA

(Apneic Spells)

This condition is characterized by intermittent respiratory pause for more than 20 seconds or apnea (sudden cessation of respiration) followed by cyanosis, bradycardia and limpness with unresponsiveness to tactile stimuli.

Etiopathogenesis

Predisposing conditions include LBW (under 1,500 g) and/or gestation under 32 weeks, HMD, aspiration, pneumonia, pulmonary hemorrhage, congenital heart disease, birth trauma, maternal sedation, accidental injection of local anesthetics during labor, tracheoesophageal fistula, diaphragmatic hernia, choanal atresia, Pierre Robin syndrome, hyperbilirubinemia, hypoglycemia, acidosis, dehydration, septicemia and methemoglobinemia.

Triggering factors include frequent handling, environmental heat, rapid rewarming, vigorous suction, sudden flexion of neck and lung inflation (head paradoxical reflex). The fundamental pathologic defect appears to be an immaturity of the medullary respiratory center which lacks effective respiratory drive.

Diagnosis

It is primarily clinical and conditions such as periodic breathing, cyanotic spells, convulsions, esophageal atresia, HMD, aspiration pneumonia, diaphragmatic hernia and congenital heart disease should be considered in the differential diagnosis.

Treatment

If cutaneous stimulation and artificial respiration fail to initiate breathing, a respiratory stimulant, theophylline 5 mg/kg (IV) followed every 8 hourly by 2 mg/kg (IV or 0) may bring about gratifying response. Caffeine citrate (IV) is an equally good alternative.

Doxapram, 1–2.5 mg/kg (IV infusion), may prove effective in apnea refractory to xanthines. Supportive measures include nursing in an incubator to maintain temperature at the lower end of the environment range, oxygen inhalation, IV drip of 10% glucose, correction of hypoglycemia, hypocalcemia, acidosis and antibiotic therapy when apneic attacks manifest after 3 days of birth.

Prognosis

Survivors, especially with immaturity, show high incidence of brain damage.

STRIDOR

See Chapter 44 (Pediatric Ear, Nose and Throat {ENT} Problems).

NEONATAL SHOCK

The term denotes a clinical state of poor perfusion of the body tissues so much and so that the body demands are not adequately met as a result of either great increase in oxygen consumption and/or great decrease in oxygen delivery.

Etiopathogenesis

The fundamental problem is sudden fall in arterial blood pressure as a result of factors affecting the cardiac output or myocardial contractibility (severe hypoxia, toxins, anaerobic metabolites, toxins, hyperkalemia) and peripheral circulatory resistance (vascular wall tone and viscosity, blood volume). The immediate response of body is to shunt blood to brain and myocardium and to cut down blood supply to skin, kidneys and GIT through vasoconstriction. Box 17.21 gives the broad etiology of neonatal shock.

Classifications

- **Etiologic:** Hypovolemic, distributive and cardiogenic
- **Based on magnitude of cardiac dysfunction:** Compensated, decompensated and irreversible
- **Based on cardiac output and flow:** Low cardiac output and high cardiac output
- **Advanced trauma life support classification:**
 - **Class 1:** Upto 15% blood loss
 - **Class 2:** 20–25% blood loss
 - **Class 3:** 30–35% blood loss
 - **Class 4:** 40–50% blood loss.

Box 17.21 Etiology of neonatal shock

Hypovolemic shock

- **Blood loss:** Antepartum (twin to twin transfusion, fetomaternal transfusion, placenta previa), intrapartum (ICH, birth trauma, excessive bleeding from umbilical vessels) and postpartum (DIC, IVH)
- **Fluid and electrolyte loss:** Vomiting, diarrhea, phototherapy, hyperthermia, poor fluid intake, iatrogenic renal disease and abdominal surgery

Distributive shock

- **Infections:** Septicemia
- **CNS:** Trauma (neurogenic shock) and HIE
- **Drugs:** Phenobarbital, muscle relaxants and anesthetics

Cardiogenic shock

- **Myocardial dysfunction:** CCF, viral myocarditis, cardiomyopathy, arrhythmias, myocardial depressants (hypoglycemia, acidosis, sepsis)
- **Outflow (mechanical) obstruction:** Pneumo or hemopericardium, tension pneumothorax, diaphragmatic hernia, severe interstitial emphysema and pulmonary embolism
- **Congenital heart disease:** TOF (severe), TOGA, HLHS, TA, PDA, AS, COA, PA with intact ventricular septum.

Abbreviations: ICH, intracranial hemorrhage; DIC, disseminated intravascular coagulation; HIE, hypoxic-ischemic encephalopathy; TA, tricuspid atresia; CNS, central nervous system; CCF, congestive cardiac failure; TOF, tetralogy of fallot; IVH, intraventricular hemorrhage; TOGA, transposition of great arteries; HLHS, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; COA, coarctation of aorta; PA, pulmonary atresia; AS, aortic stenosis.

Clinical Features

These include marked pallor despite adequate hematocrit, lethargy, irritability, hypotonia, circumoral grayish discoloration, cold-clammy skin of limbs, difference of more than 2.5°C between core and surface temperatures, capillary refill time more than 2 seconds, tachycardia, tachypnea and sclerema. In addition, systemic manifestations due to involvement of CNS, CVS, respiratory system, GIT and kidneys may be present.

Complications

These include DIC, shock lung, acute renal failure (ARF), NEC, hemorrhage (pulmonary, IVH, periventricular hemorrhage {PVH}).

Diagnosis

It is based on a carefully recorded history and physical examination with special reference to predisposing causes, blood pressure (intraarterial line should be preferred over Doppler method), focus of infection, peripheral circulation and cardiopulmonary status. Special investigations include hematocrit, CBC, coagulation profile, serum calcium, glucose, blood urea nitrogen (BUN), creatinine, blood culture and sepsis screen, pulmonary artery catheterization for liver function test (LFT), central venous pressure (CVP), leukocyte alkaline phosphatase (LAP) and SVR, arterial blood gases, ECG, chest X-ray and echocardiography.

Treatment

Aggressive therapeutic approach consists of maintaining CVP at 5–8 cm of water, monitoring heart rate, oxygenation and BP round the clock, correcting hypoxia, acidosis or hypoglycemia, correcting dyselectrolytemia, blood transfusion, vitamin K, antibiotics, inotropic drugs (digoxin, dopamine, isoproterenol, dobutamine) and massive doses of steroids. Direct current cardioversion in case of cardiogenic shock and pericardiocentesis in case of pneumopericardium are indicated.

Prognosis

With modern treatment, around 50% patients can be saved.

INFECTIONS IN THE NEWBORN

Quite a number of factors contribute to uniqueness of neonatal infections (Box 17.22).

The term **intrauterine infection** refers to infection acquired in utero. The TORCH group of infections (syphilis, toxoplasmosis, others like HIV, hepatitis B virus {HBV}, etc, rubella, cytomegalovirus and herpes simplex) HIV/AIDS belong to this category.

The term **perinatal infection** refers to an infection that is acquired just before or during delivery from the mother. Such an infection may occur from the organisms colonizing the birth passage (group B Streptococci, *Gonococci*, *E. coli*, *Listeria monocytogenes*, *Chlamydia*, Mycoplasma, Herpes simplex and Enteroviruses), or as a result of maternal to

Box 17.22

Factors contributing to uniqueness of neonatal infections

- Diverse modes of transmission from mother to the fetus or neonate—hematogenous transplacental and vertical postnatal.
- Disturbed immunocompetence leading to reduced capability to respond to infection.
- Coexistence of one or more diseases of the neonate complicating the diagnosis and treatment of infection.
- Remarkably variable manifestations of neonatal infections, the expression depending on time of exposure in utero, size of inoculum, immune status and etiologic agent.

fetal transfusion at delivery (HBV and HIV). The bacterial invasion of the amniotic fluid, usually as a consequence of PROM, is termed **amniotic infection syndrome**. Besides this syndrome, difficult or traumatic delivery as also premature delivery may also be accompanied by perinatal infections. At times, a perinatal infection may actually manifest after some interval following birth.

The term **early neonatal infection** should be limited to perinatal infection with manifestations occurring within 72 hours of birth. The term **late-onset infection** is applied to sepsis occurring after 72 hours. The term **post neonatal infection** refers to infection acquired after 28 days of life.

Prematurity and LBW, intubation and umbilical catheterization are accompanied by an increased risk of bacterial infection. This kind of infection is also called **late-onset neonatal infection**. Neonatal infections that develop later than 48–72 hours after birth and during stay in the hospital are considered **nosocomial**.

The organisms responsible for postnatal neonatal infection include *E. coli*, *Klebsiella*, *Pseudomonas*, *Aerobacter*, *Enterococci*, *Proteus*, *Staphylococcus aureus* and *Candida*. Umbilicus is the most common route of entry of the organism into the body. Alternatively, it may invade the body through skin or mucosa (usually in the presence of a breach or cut). Box 17.23 outlines predisposing factors for postnatal neonatal infections. Box 17.24 outlines preventive measures for nosocomial neonatal infections.

Superficial Infections

Neonatal Conjunctivitis

Neonatal conjunctivitis (Fig. 17.47) may be caused by agents such as *Chlamydia trachomatis*, *Neisseria gonococcus* and *Staphylococcus aureus*. Uncommon causative agents include streptococcus (group A and B), *Pseudomonas aeruginosa* and herpes virus hominis type 2. Use of silver nitrate drops may also cause conjunctival inflammation which manifests within 6–12 hours after birth and disappears by 24–48 hours.

Box 17.23

Preventive factors for neonatal infections

- Low birth weight/prematurity
- Contaminated environments in uterus
- Infected birth passages → infected postnatal environments
- Congenital anomalies
- Hospital procedures
- Artificial feeding
- Male sex.

Box 17.24**Prevention of postnatal neonatal infections (nosocomial)**

- Proper washing of hands and forearms with soap and water
- A 2-minute scrub before entering nursery, 15-second scrub between two neonates are strongly recommended
- Avoidance of overcrowding
- Minimum handling of the infants
- A check on the entry of individuals harboring infection, including carriers, into the nursery
- Change in hand-washing solutions and protocols
- Proper cleansing and maintenance of nursery
- Equipment sterilization
- Proper cleansing of babies and the cord care in particular
- Use of separate/disposable kits for infants
- Chemoprophylaxis as, and when indicated
- Breastfeeding.



Fig. 17.47: Neonatal conjunctivitis. Note edema of the eyelids with chemosis. Delay in instituting proper treatment may lead to involvement of the deeper layers of conjunctiva as also cornea.

Treatment

Simple sticky eyes with no purulent discharge, a common observation during the first couple of days, needs only saline irrigation or sulfacetamide drops (10%).

Purulent conjunctivitis due to Gram-positive cocci needs to be treated with penicillin (2,500 units/mL), framycetin or chloramphenicol eye drops.

Gonococcal ophthalmia is treated with (it is responsible for profuse purulent discharge) systemic penicillin therapy (100,000–150,000 units/kg/day in 2 or 3 divided doses) and penicillin, gentamicin or chloramphenicol eye drops. A single dose of kanamycin (75–150 mg IM), is also effective. Currently, the treatment of choice is ceftriaxone, 25–50 mg/kg/day for 7 days.

Conjunctivitis caused by *Chlamydia trichomatis* (inclusion blenorrhea) needs treatment with 10% sulfacetamide eye drops. In case of poor response, oral erythromycin should be given.

Pyoderma

Superficial skin eruptions, usually caused by *Staphylococcus aureus* and *albus* result from contaminated hands of the personnel responsible for caring the neonate. No treatment other than local application of triple-dye is indicated.

Pyoderma, manifesting as pustules over scalp, neck, axillae and groins may spread to cause abscesses, osteomyelitis, parotitis, septicemia and, what is worst, remarkable erythema, bullae and exfoliation (pemphigus neonatorum).

Treatment of these lesions is puncturing followed by application of triple dye. Any suggestion of spread of infection is an indication for administering erythromycin or some antibiotic agent.

Oral Thrush (Moniliasis, Candidiasis)

This condition, caused by *Candida albicans*, may occur even in healthy neonates from the infected birth passage during delivery, infected feeding equipment and prolonged antibiotic therapy.

The lesions, usually preceded by redness of oral mucosa and tongue are characteristically discrete whitish patches/spots over the tongue mucosa, gums and lips; extension over to the posterior oropharynx may occur, leading to swallowing difficulties. Involvement of the perianal region is frequent, so is the monilial diarrhea. The lesions are difficult to be removed by scraping. Response to local application of gentian violet (0.5%), nystatin (2,00,000 units/5 mL), or cotrimazole, after each feed, is gratifying. A 5–7 days course suffices.

Noma Neonatorum

Occasionally, *Pseudomonas aeruginosa* infection may cause superficial gangrenous lesions involving nose, lips, mouth, anus, eyelids and scrotum. The condition proves fatal within a few days.

Septic Umbilicus (Omphalitis)

Umbilical infection in the newborn is a common problem. The etiologic factors include poor sanitary conditions and local application of unsterile dressings. *E. coli* and *Staphylococcus* are the most common organisms responsible for it. It may present as:

- Slight purulent discharge from localized infection of the stump
- Umbilical abscess
- Periumbilical cellulitis
- Umbilical gangrene.

Even septicemia and neonatal tetanus may well be regarded as forms of umbilical sepsis. If left untreated or inadequately treated, localized infection may be accompanied by formation of a pinkish, rounded, berry-like mass with granulation tissue (umbilical granuloma). It is responsible for persistent serous discharge for several weeks or even months.

- **Prevention:** It lies in aseptic care of the umbilicus, including its cutting. It is best left uncovered rather than dressed with a binder.

- **Treatment:** It consists of administering a broad-spectrum antibiotic and local application of triple-dye, gentian violet paint or a powder/cream containing bacitracin and neomycin. An umbilical granuloma needs cauterization by touching it with silver nitrate or copper sulfate crystal.

Systemic Infections

Neonatal Sepsis (Nns)

Sepsis is a serious neonatal problem. Failure to recognize and treat it early is met with high mortality. It is termed **early-onset neonatal sepsis (EONS)** when occurring in first 72 hours and **late-onset neonatal sepsis (LONS)** when occurring at or after 72 hours.

Etiopathogenesis

Infection may be contracted antenatally, or during or after birth. The portal of entry in vast majority is the umbilical vein. At times, GIT or some other infection may also cause sepsis. Like anywhere in the world, in India too, the microbiologic pattern of neonatal septicemia varies from time to time and from institute to institute. The neonatal units must, therefore, have an ongoing review of the causative organisms and their antibiotic sensitivity pattern from time to time. Predisposing factors and etiologic pathogens are listed in Box 17.25.

Clinical Features

- Except when the infant is infected in utero, during delivery or immediately after birth, manifestations usually become evident towards the fag end of the first week or in the second week.

Box 17.25

Predisposing factors and etiologic pathogens in NNS

Predisposing factors

• EONS

- Febrile maternal illnesses
- Prematurity/LBW
- Prolonged rupture of membranes
- Frank amnionitis
- Multiple vaginal examination
- Difficult/prolonged labor
- Meconium aspiration
- Instrumentation
- Equipment (use of catheters, respirator, resuscitator, feeding bottles, solutions for cold sterilization, incubator, face masks and white aprons, etc)
- Mouth to mouth breathing and
- Umbilical sepsis. It usually manifests as pneumonia. Septicemia and meningitis are infrequent in EONS.

• LONS

- Septic nursery environment
- Prematurity/ LBW
- Erratic cord care causing umbilical sepsis,
- Skin infections(pyoderma)/breach from needle pricks and IV drip, artificial feeding.
- Handling by medical personnel, including doctors and nurses, may. It usually manifests as septicemia, pneumonia or meningitis

Etiologic pathogens

- **EONS:** *E. coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*.
- **LONS:** *Streptococcus hemolyticus*, *Staphylococcus albus*, *Listeria monocytogenes*, *Enterobacter*, *Alkaligenase fecalis*, *Proteus mirabilis*, *Salmonella typhimurium*, *Citrobacter*, *Serratia*, *Bacteroides sp*, *Peptococcus*, *Peptostreptococcus*, *Clostridium perfringens* and *Candida*.

- These are identical despite varying causative agents and may vary from inapparent or silent to fulminant, depending on severity of infection, maturity and birth weight of the infant.
- Earliest manifestations may be just lethargy, refusal of feeds, vacant listless look, circumoral cyanosis, vomiting, irritability, restlessness apneic spells and cyanosis.
- Loose motions, abdominal distention, fever or hypothermia (latter is more common and more dangerous), failure to gain weight, pallor, jaundice, respiratory distress and skin eruptions are other prominent features. Umbilicus may be septic.
- Hepatosplenomegaly and pallor are present in a proportion of cases.
- Associated meningitis is frequent (20–30% cases). The occurrence of convulsions, high-pitched cry, blank listless appearance, bulging anterior fontanel and neck retraction should arouse suspicion of its existence.
- Depending on involvement of various systems, there may be pneumonia, (LIT), bleeding and NEC, etc.
- NNS should be considered overwhelming in the presence of sclerema, shock, DIC and acute kidney injury (renal failure).

Diagnosis

- **Clinical:** It is primarily clinical, warranting high index of suspicion. One should take advantage of the clinical clues for probable etiologic diagnosis (Table 17.11). Differential diagnosis is from conditions such as hypoglycemia, hypo and hyperthermia, heart failure, hypoxia and late metabolic acidosis.
- **Investigations:** Blood culture, the gold standard provides definitive diagnosis. However, in clinically highly probable cases of NNS, availability of its report need not come in the way of initiating appropriate antimicrobial therapy.
- **Sepsis screen** (Box 17.26) helps in confirming or ruling out NNS. Presence of two or more parameters means a positive sepsis screen. A repeat screen is indicated in case of a negative result after 12 hours; every 48 hours in ventilated neonates.

Table 17.11: Clinical clues to etiologic diagnosis

Clues	Organisms
Superficial infections such as pyoderma, abscess, conjunctivitis, umbilical sepsis, osteomyelitis; onset of manifestations after 72 hours of birth	<i>Staphylococcus</i>
Grayish-black gangrenous lesions over skin	<i>Pseudomonas</i>
Peripartum flu-like maternal illness, gastroenteritis, meconium-stained liquor amni, baby is unwell right at birth with limpness and develops respiratory difficulty, apneic spells, rash and hepatosplenomegaly on the first day	<i>Listeria</i>
Maternal fever during labor, prolonged rupture of membranes (PROM); respiratory distress within 3 hours of birth, apneic spells, shock	<i>Streptococcus group B</i>

Box 17.26 Sepsis screen for NNS

- TLC less than 5000/mm³
- Band cell/neutrophil ratio more than 0.16
- Micro ESR more than 15 mm
- Positive CRP.

Abbreviations: TLC, total leukocyte count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NNS, neonatal sepsis.

- **Lumbar puncture** is of value if meningitis is suspected. While interpreting cerebrospinal fluid (CSF) biochemistry and microscopy, normal values for term and preterm neonates should be borne in mind.
- **Other useful investigations** include chest X-ray, blood sugar, urine for routine and culture and serum bilirubin.

Treatment

Institution of timely appropriate treatment, both specific and supportive is mandatory for good outcome.

Specific antimicrobial therapy

- **In early septicemia**, there is no need to wait for outcome of blood culture to initiate antimicrobial therapy. However, in a stable neonate, it is of help to wait for the outcome of sepsis screen before instituting therapy. In order to cover most Gram-positive and negative pathogens, ampicillin + gentamicin/amikacin is the first line recommendation. In low probability of ampicillin resistant cases, the choice is ampicillin or cloxacillin + gentamicin/amikacin is the second line recommendation. In high probability of ampicillin resistant cases, the choice is a third generation cephalosporin (cefotaxime) + gentamicin/amikacin is the third line recommendation. In case of accompanying meningitis, a third generation cephalosporin (cefotaxime) + ampicillin/amikacin make the ideal therapy.
- **In late-onset septicemia**, first line therapy should be ampicillin + gentamicin/amikacin and the second line cefotaxime + amikacin.

If *Staphylococcus* is suspected, cloxacillin needs to be added. For resistant *Staphylococcus*, coamoxyclov or vancomycin is the best. In nosocomial septicemia (*Staphylococcus*, *Klebsiella*, *Pseudomonas*), ceftazidime/cefepime + netilmicin make an excellent combination. Nevertheless, vancomycin is the best. If the culture and sensitivity report warrants a change in the antimicrobial therapy, it should be made. Minimum duration of chemotherapy varies with the type of NNS (Box 17.27).

Box 17.27 Minimum duration of antimicrobial therapy in NNS

- Uncomplicated sepsis: 10–14 days
- With UTI: 14 days
- With meningitis: 3 weeks
- With osteomyelitis: 6 weeks
- Presumptive sepsis which fails to be confirmed by blood culture or follow-up observations: 5 days.

Abbreviations: UTI, urinary tract infection; NNS, neonatal sepsis.

Supportive Measures

- These include IV line/drip for:
 - Infusion of normal saline or ringer lactate, often with dopamine and dobutamine, to improve perfusion
 - Infusion of 10% glucose
 - Infusion of potassium once the neonate has attained normal urine flow
 - Maintenance fluid and electrolyte balance.
- Maintenance of optimal body temperature, i.e. 36.5–37.5°C
- Oxygen by hood, mask or bag and mask ventilation for hypoxia, cyanosis or grunting
- Nasal saline drops to clear nasal block, if any
- Blood transfusion (packed cells) for anemia and shock; additionally, it may also boost defense mechanism (immunity) through opsonins and polymorphs
- Optimal nutrition through mother's expressed milk; parenteral nutrition when enteral feeding is not allowed for prolonged period
- Vitamin K; 1 mg IM.

Promising new therapeutic modalities include high dose intravenous immunoglobulin (IVIG), exchange transfusion, granulocyte transfusion, fibronectin and cytokines. Available cytokines are:

- Granulocyte colony stimulating factor (G-CSF);
- Granulocyte macrophage colony stimulating factor (GM-CSF);
- Tumor necrosis factor- α (TNF- α);
- Gamma interferon.

Indications of such a therapy include poor response to appropriate antibiotic therapy with persistent neutropenia, depleted marrow neutrophil storage pool (NSP) or disturbance in myeloid progenitor proliferation.

Its risks are transmission of HIV and cytomegalovirus. In case of scleroma, endotoxic shock and meningitis, administration of hydrocortisone may be considered. In DIC, fresh blood transfusion followed by heparin and platelet and fibrinogen therapy is indicated. Prolonged chemotherapy should be supplemented with vitamin K and other vitamin therapy.

Prognosis

Close monitoring, timely institution of appropriate antimicrobial therapy and intensive supportive care are the key factors in survival of the neonates with sepsis. Despite availability of newer broad-spectrum chemotherapy, almost 25–50% of neonates with sepsis die. Mortality is higher in:

- Early-onset (within 72 hours of birth) septicemia
- Presence of serious congenital anomalies
- Presence of meningeal involvement
- Gram-negative septicemia
- *Pseudomonas* infection where it is worst
- LBW and premature babies.

NECROTIZING ENTEROCOLITIS (NEC)

This is a poorly understood disorder of the newborn in which the small preterm baby develops lethargy, vomiting, bloody diarrhea, distention of abdomen, hypothermia and apnea. Terminally, he may go into cardiovascular collapse.

Box 17.28 Modified Bell's three stages of NEC

1. **Stage 1 (suspected NEC):** Features include unstable temperature, apnea, bradycardia, lethargy, mild abdominal distention, vomiting and blood in stools. Abdominal film shows mild intestinal distention.
2. **Stage 2 (proven NEC):** Signs of Stage 1 plus diminished bowel sounds; abdominal tenderness may be present. Abdominal film shows dilated loops of intestines.
3. **Stage 3 (advanced NEC):** Signs of Stages 1 and 2 plus hemodynamic instability, redness of abdominal wall, peritonitis; intestinal perforation with pneumoperitoneum.

Abbreviation: NEC, necrotizing enterocolitis.

Etiology

The condition is encountered usually in LBW babies born before term (usually less than 32 weeks). It may however, occasionally, develop even in normal fullterm babies. Premature LBW/term ratio is 9:1. It is believed to be the outcome of interaction between intestinal mucosal injury, luminal bacteria, enteral feedings and immature host response.

Predisposing factors include maternal fever, amniotitis, sepsis, respiratory distress syndrome (usually of mild type), HIE, exchange transfusion and oral feeding with high osmolar (hypertonic) stuff.

Clinical Features

Manifestations appearing after a week of birth are those of sepsis e.g. lethargy, vomiting, bloody diarrhea, distention of abdomen, hypothermia and apnea. Currently, three stages are recognized (Box 17.28).

Investigations

Abdominal X-ray shows air-fluid levels, dilated loops of gut, separation of loops of gut and linear streaks of intraluminal air, pneumatosis intestinalis (Fig. 17.48) which confirm the diagnosis. Blood, CSF and stool cultures are needed.

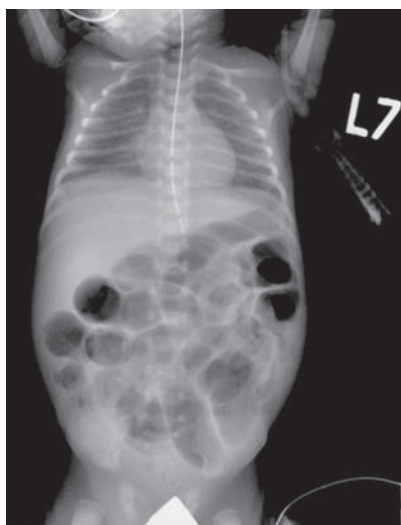


Fig. 17.48: Necrotizing enterocolitis: Note the pneumatosis intestinalis along with distended loops of bowel (which establishes the diagnosis in a suspected case scenario) in the neonate with progressively increasing abdominal distention.

Treatment

Treatment comprises of:

- Temporary withdrawal of oral/enteral feeds
 - Antimicrobial cover
 - Intravenous fluids/parenteral nutrition
 - Vasopressor agents for shock
 - Plasma and platelet transfusion
 - Supportive measures to maintain temperature.
 - Surgical intervention in case of intestinal perforation.
- Figure 17.49 gives an algorithmic approach to NEC.

Prognosis

Prognosis is bad. High mortality may result from complications such as perforation, abdominal wall cellulitis and pneumoperitonitis.

Sequelae

These include:

- Intestinal strictures
- Colonic stenosis
- Malabsorption from short gut syndrome
- Liver disease associated with parenteral nutrition in infants undergoing surgical therapy
- Growth delay
- Neurodevelopmental problems
- Recurrence of NEC.

NEONATAL MALARIA

On account of the protection provided by the transplacental passage of maternal IgG antibodies which may act as opsonizing agents or block the merozoitic invasion of erythrocytes so that the erythrocytic (hepatic) phase is absent, neonatal malaria is infrequent in highly malarious areas.

Etiology

Neonatal malaria is of three types:

1. **Congenital:** It is due to transplacental transmission of the malarial parasite and is rare since placenta, as a rule, is supposed to act as a barrier to such a transfer. In a span of over two decades, we could diagnose it in only 50 instances, though we have all along been actively looking for it.
2. **Transfusion malaria:** It follows infected blood transfusion.
3. **Naturally-acquired malaria:** It results following an actual bite of a previously infected female anopheles mosquito.

Clinical Features

Clinical manifestations include unexplained pyrexia with hepatosplenomegaly, anemia, slight jaundice, poor feeding, irritability and jitteriness. IUGR may be seen in congenital malaria, especially if the baby is first born and was affected early in intrauterine life.

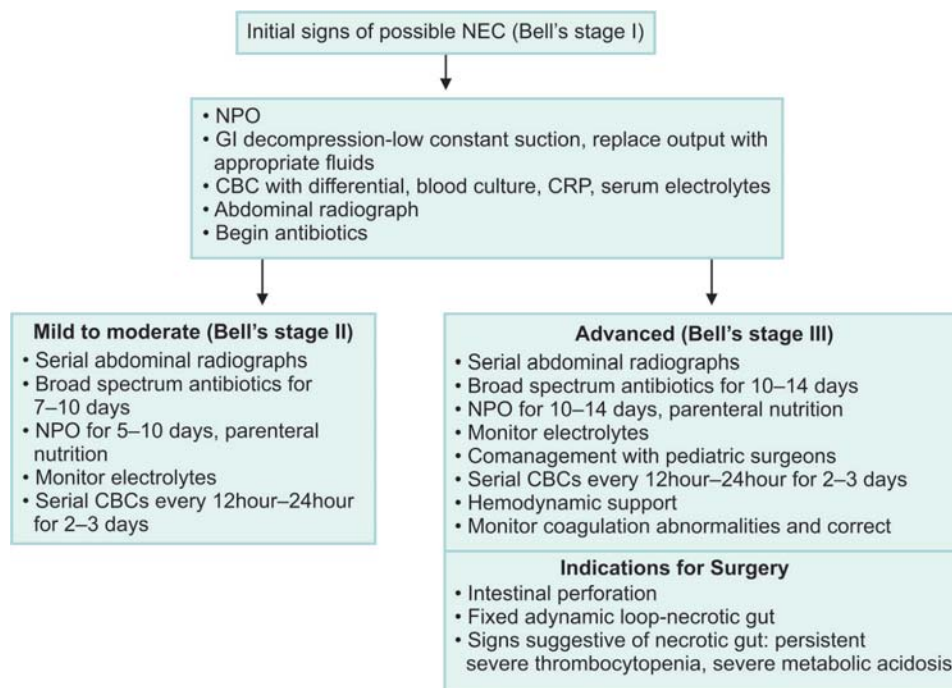


Fig. 17.49: Necrotizing enterocolitis. An algorithmic approach to NEC.

Source: Recent Advances in Pediatrics Special-25.

Abbreviations: NEC, necrotizing enterocolitis; NPO, nil per orally; CRP, C-reactive protein; CBC, complete blood count; GI, gastrointestinal.

Diagnosis

The points favoring diagnosis of congenital malaria are:

- Malaria in the mother during pregnancy.
- Manifestations occurring before the minimal incubation period (12–16 days for *P. vivax* and *P. ovale*, 10–13 days for *P. falciparum* and 27–37 days for *P. malariae*).
- Absence of history of blood transfusion.

Treatment

Chloroquine, 10 mg/kg (O) or 5 mg/kg (IM), should be given after taking blood for peripheral film. The same (half dose) may be repeated after 6 hours, 24 hours and 48 hours. Supportive treatment directed at controlling fever, raising hemoglobin level and maintaining water and electrolyte balance and nutrition is also warranted.

Prophylaxis

- Timely treatment of maternal malaria and even empirical administration of chloroquine to pregnant mothers during the third trimester.
- Blood for transfusion must be tested for malarial parasite.
- Standard measures for control and eradication of malaria.

TETANUS NEONATORUM

Neonatal tetanus results from contamination of the umbilical stump following cutting of the cord with an infected blade, knife or scissors or application of cow dung, etc. on it—a common practice with untrained traditional birth attendants (UTBAs).



Fig. 17.50: Neonatal tetanus. Note the gross trismus, leading to feeding difficulties.

Manifestations usually occur between 2 days and 2 weeks of age. To start with, the baby has unexplained crying, refusal of feeds and apathy. On forcing the feed, reflex spasm of masseters, pharyngeal muscles leads to trismus (lock jaw) (Fig. 17.50), dysphagia and choking. Spasms of limbs and generalized rigidity with opithotonos in extension follow. Reflex laryngeal spasm may cause apnea and that of respiratory muscles the cyanosis. Continued spasm may lead to pyrexia, tachypnea, tachycardia, dehydration and acidosis. Superimposed infections are common. India stands declared as neonatal tetanus-free in 2015.

HEMORRHAGIC DISEASE OF THE NEWBORN

This entity is discussed in Chapter 32 (Pediatric Hematology).

NEONATAL JAUNDICE

Jaundice is a common manifestation among newborns. Unlike adults in whom it is clinically detectable with a serum bilirubin of less than 2 mg/dL, in neonates it is apparent only when serum bilirubin is less than 5 mg/dL. Approximately, it is encountered in about 75% of them with a relatively higher incidence in preterm neonates.

Etiologic Considerations

- **Classification based on time of onset:** Box 17.29 lists the important causes of jaundice in accordance with the time of its appearance.
- **Classification based on conjugation of bilirubin:** Conjugate hyperbilirubinemia which is usually secondary to hypertrophic biliary atresia or neonatal hepatitis in newborns has already been discussed in details in Chapter 30 (Hepatology and Pancreatology). Box 17.30 gives etiology of unconjugated hyperbilirubinemia.

Frequently Encountered Types of Jaundice

Physiological Jaundice (Fig. 17.51)

Most of the neonates (50–60 % fullterm, 70–80% preterm) develop it on account of:

Box 17.29

Important causes of neonatal jaundice based on age of onset

First day

- Rh and ABO incompatibilities (hemolytic disease of the newborn)
- Intrauterine infections like toxoplasmosis and cytomegalic inclusion disease
- G6PD deficiency
- Hereditary spherocytosis
- Drug administration to mother (vitamin K, sulfisoxazole, salicylates)
- Homozygous alpha-thalassemia

Second and third days

- Physiologic hyperbilirubinemia of newborn
- Birth asphyxia
- Cephalhematoma
- Acidosis
- Hypothermia
- Hypoglycemia
- Drugs
- Familial nonhemolytic icterus as in Crigler-Najjar disease, Gilbert disease, Dubin-Johnson syndrome.

Fourth to seventh days

- Septicemia
- Syphilis
- Toxoplasmosis
- Cytomegalic inclusion disease
- Extrahepatic atresia of bile duct
- Breast milk jaundice.

After first week

- Septicemia
- Extrahepatic atresia of bile duct
- Hereditary spherocytosis
- Neonatal hepatitis
- Drug-induced hemolytic anemia
- Galactosemia.

Persistent jaundice during first month

- Inspissated bile syndrome
- Cretinism
- Congenital hypertrophic pyloric stenosis.

Box 17.30 Causes of unconjugated hyperbilirubinemia

Physiologic

Pathologic

Increased production of bilirubin

- **Hemolytic disease of the newborn:** Rh isoimmunization, ABO incompatibility, minor blood group incompatibility
- Hereditary spherocytosis
- **Nonspherocytic hemolytic anemia:** G6PD deficiency, pyruvate kinase deficiency, alpha-thalassemia
- **Acquired hemolysis disorders:** Vitamin K3-induced hemolysis, microangiopathies
- Septicemia
- **Increased enterohepatic circulation:** Intestinal obstruction, congenital hypertrophic pyloric stenosis, meconium ileus paralytic ileus, Hirschsprung disease

Decreased clearance of bilirubin

- **Inborn errors of metabolism:** Familial nonhemolytic jaundice (Crigler-Najjar syndrome) type I and II, Gilbert disease
- **Medications:** Vitamin K₃
- **Hormones:** Breast milk jaundice, hypothyroidism, hypopituitarism.

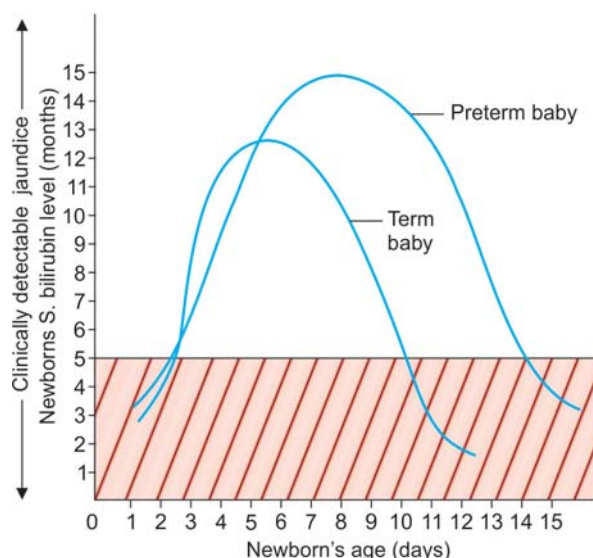


Fig. 17.51: Physiological jaundice: Time table in term and preterm neonates. Note that onset of jaundice is about the same time in both, i.e. after 24 hours of birth. Serum bilirubin level at which jaundice becomes clinically detectable is 5 mg/dL.

- Increased production of bilirubin (outcome of low lifespan of fetal red blood cells (RBC) and very high hemoglobin level in the neonate)
- Decreased hepatic uptake of bilirubin from plasma
- Defective bilirubin conjugation
- Defective bilirubin excretion
- Increased enterohepatic circulation.

Physiological jaundice is a self-limiting condition. In term infants, it appears on second or third day (between 30 and 72 hours) and reaches peak on 4th or 5th day. It is generally mild, the serum bilirubin seldom exceeding 12–15 mg%. It disappears by 10th day (Fig. 17.50).

In case of the preterm baby, physiological jaundice may appear little earlier (but always after 24 hours), may be relatively deeper (upto 15 mg/dL) and reaches peak on 6th or 7th day. It disappears by 14th day (Fig. 17.50).

310 Physiological jaundice is a benign condition, needing no treatment, except in preterm infants in whom phototherapy and exchange transfusion may be needed to safeguard against kernicterus. Nevertheless, the infant needs to be closely followed up for undue rise or persistence of hyperbilirubinemia. In the latter situation, he should be investigated for pathologic jaundice.

Exaggerated Physiological Hyperbilirubinemia

In certain situations such as (infant of a diabetic mother, IVH, cephalhematoma, hypothyroidism, inhibitors in breast milk, hypoxia, CHD, delayed passage of meconium, congenital infections, polycythemia, certain drugs), physiological jaundice may be exaggerated and/or prolonged beyond the usual limits. This is termed as **exaggerated physiologic jaundice** or **hyperbilirubinemia**.

Pathological Jaundice

(Unconjugated Hyperbilirubinemia)

The neonatal jaundice not conforming to time table or serum bilirubin level typical of physiological jaundice is termed **pathological**. Immaturity, blood group incompatibilities, intrauterine and postnatal infections, G6PD deficiency, etc. should be considered. Table 17.12 lists major differences between physiological and pathological jaundice.

Breastfeeding Jaundice

Exclusively breastfed neonates have a tendency to develop higher serum bilirubin levels during first few days of life. The cause may be insufficient lactation leading to inadequate feeding, dehydration and hemoconcentration. It needs no intervention.

Breast Milk Jaundice

A small proportion of exclusively breastfed infants also tend to develop persistence of physiologic jaundice or exaggerated jaundice (serum bilirubin touching 18–20 mg/dL in some) in the second week of life as a result of substances such as 3- α , 20- β pregnanediol and free fatty acids in mother's milk which inhibit conjugation of bilirubin. It resolves on its own. Occasionally, undue anxiety in the parents may warrant temporary withdrawal of breastfeeding just for 2–3 days.

Table 17.12: Neonatal jaundice. Comparison of clinical features of physiological and pathological jaundice in neonates

Parameter	Physiological jaundice	Pathological jaundice
Onset	More than 24 hours of birth	Less than 24 hours of birth
Serum bilirubin rise	Slow	Rapid: 0.5 mg/hour or 10 mg/24 hours
Peak serum bilirubin	Upto 12 mg/dL in term and 15 mg/dL in preterms	More than 15 mg/dL in term and 21 mg/dL in preterms
General condition	Healthy	Sick—sepsis, blood group incompatibility Not so sick—neonatal cholestasis

Diagnostic Approach

History

The following points should be particularly noted:

- Maternal and family history with special reference to maternal infections during pregnancy, drugs given during pregnancy or labor, previous sibling(s) affected by jaundice or anemia, diabetes and previous blood transfusions.
- Ethnic group of the parents and ancestors; history of consanguinity for hemoglobinopathies.
- Delayed passage of meconium.
- Time of onset of jaundice.
- Whether jaundice decreasing or increasing in intensity
- General condition of the infant—whether healthy, having no feeding difficulty, no fever, no rash?
- Type of feeding—whether breastfed?

Clinical Examination

- Gestational age, activity and general condition of the infant.
- Whether umbilicus is septic?
- Whether any evidence of hemorrhage and petechiae, etc.?
- Any congenital malformation?
- Any neurologic finding?
- Pallor.
- Cephalhematoma.
- Hepatosplenomegaly.
- Color of urine and stool.
- Clinical detection and grading of severity of jaundice (Box 17.31).

Laboratory Investigations

- Serum bilirubin, both direct and indirect. Conjugated (direct) bilirubin less than 0.2 mg % or more than 20% of total should be considered abnormal
- ABO and Rh blood grouping of mother as well as baby
- Hemoglobin/peripheral smear
- Reticulocyte count
- Coombs test of mother as well as baby
- Blood culture
- Liver function tests
- G6PD enzyme studies.

Principles of Management

Phototherapy and **exchange transfusion** are the two major effective therapeutic modalities available today. Additional options include pharmacotherapy in the form of phenobarbital, agar-agar, albumin infusion, n-mesoporphyrin and charcoal, etc.

Phototherapy

First introduced by Kramer, phototherapy has emerged as the most widely used tool for treating unconjugated pathologic hyperbilirubinemia.

Indications

These are listed in Table 17.13.

Box 17.31**Clinical methods of detection of neonatal jaundice****Blanching**

Blanching the skin of tip of nose, sternum, abdomen, palms and soles with digital pressure. In accordance with the Kramer's guidelines based on the observation that neonatal jaundice progresses in a cephalocaudal direction, a rough estimate of the bilirubin level can be made as follows:

- **Face:** 5 mg/dL
- **Chest and upper abdomen:** 10 mg/dL
- **Lower abdomen, thighs and upper arm:** 12 mg/dL
- **Thighs and upper arm:** 12 mg/dL
- **Legs and forearm:** 15 mg/dL
- **Palms and soles more than:** 15 mg/dL (Fig. 17.52).

Icterometer

This is a noninvasive method which is more accurate and less subjective. The tool used is a transparent plastic with five graded yellow stripes of different shades corresponding to the serum bilirubin levels. It is pressed against the tip of the nose (in case of very dark skin, gums make a better option). The color of the skin is matched with the yellow stripes to obtain the bilirubin level.

Transcutaneous bilirubinometer

This more accurate and more objective, but expensive instrument, measures the total serum bilirubin employing a photoprobe. The photoprobe is pressed against the skin of forehead or sternum (in case of very dark skin, a drop of blood on a filter paper make a better option). Following analysis by the computerized spectrophotometer, digital display of the bilirubin level is immediately made.

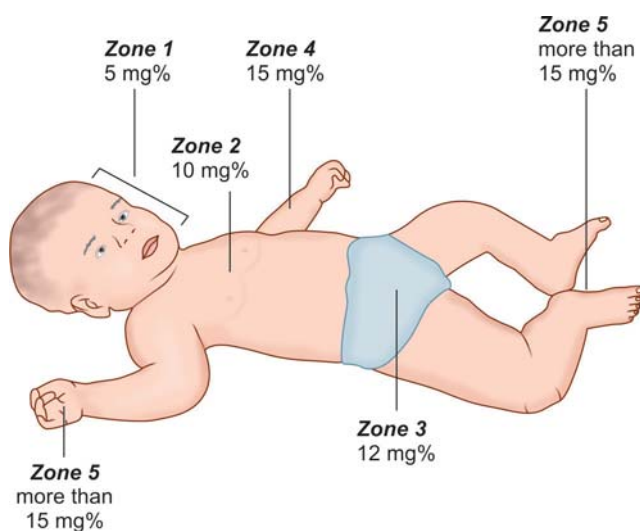


Fig. 17.52: Neonatal jaundice. Dermal zones as an index of magnitude of neonatal jaundice (level of serum bilirubin).

Table 17.13: Indications of phototherapy

Birth weight	Serum bilirubin at which phototherapy is indicated
2500 g	15 mg/dL
2000–2500 g	12 mg/dL
1500–2000 g	10 mg/dL
1000–1500 g	7 mg/dL
Less than 1000 g	5 mg/dL

Mode of Action

The value of phototherapy in lowering unconjugated hyperbilirubinemia is widely accepted.

In order to understand its mode of action, it should be remembered that bilirubin absorbs blue-green light

maximally at 460–490 nm. With light sources of this range, most of it (80%) undergoes photoisomerization to bilirubin (of better soluble form). A small portion gets oxidized to biliverdin. These are excreted in bile and to a lesser extent in urine.

That bilirubin is broken down in the skin is now well-documented. A common observation during photo-therapy is the bleaching of the exposed areas. The areas of skin that remain covered continue to have yellow touch. Whether liver also plays significant role during photoexposure is being currently investigated.

Technique

It is now generally opined that blue light is superior to white light. Though simple sunlight is useful, artificial light sources are far better. Most neonatal units employ standard length tube lights (STL) phototherapy. Alternatively, compact fluorescent lamp (CFL) phototherapy units now available in India, may be employed. These lamps can be mounted with reflectors in frames. It is claimed that these are superior to conventional (STL) units on account of smaller size, focused area, lower scatter and higher irradiance. The advantages include greater efficacy and more acceptability to nursing staff.

Such a phototherapy unit delivers about 200 foot candles of light to the infant. It can also be placed over an incubator. The only problem with blue light is that it interferes with reasonable observations of the baby. Alternatively, white day-light lamps/tubes are reasonably effective and may be employed. A unit with a combination of both blue and white light tubes may also be employed.

Length of Phototherapy

Just 24–48 hours exposure is generally long enough to bring down serum bilirubin level to safe limits. Though many authorities insist on giving continuous therapy, there is evidence to the effect that intermittent exposure is almost equally good.

Skin color is not a reliable criterion for stopping or continuing phototherapy. The yellow color of the skin disappears or regresses much earlier than the return of serum bilirubin to near normal. It is, therefore, desirable that serum bilirubin estimation is done at intervals of 12 hours. Termination of phototherapy is indicated at serum bilirubin less than 11 g/dL on 2 consecutive sittings 24 hours apart.

Special Precaution

During exposure to phototherapy, infant's eyes should always be protected with something like a mask (Fig. 17.53). This is essential to nullify chances of retinal damage. In case of the male neonate, the external genitalia too need to be covered to prevent gonadal insult.

Contraindication

Congenital erythropoietic porphyria.

Side Effects■ **Immediate**

- Loose motions (greenish or dark-brown) are due to high content of photodegeneration products



Fig. 17.53: Phototherapy in neonatal jaundice. Note the yellow discoloration of the skin. ABO incompatibility was responsible for elevation of the serum bilirubin to 16 mg% by third day in this fullterm neonate. Response to phototherapy was excellent.

- Dehydration, generally mild, occurs in some cases
- Fever (hyperthermia) or hypothermia
- Hypocalcemia
- Skin rashes are usually mild and self-limiting, disappearing rapidly
- Bronzing of skin, urine and serum (bronze baby syndrome) which may occur in conjugated hyperbilirubinemia. It disappears soon after cessation of phototherapy with no permanent sequelae
- Electric shock.
- **Delayed**
 - Retinal damage and possible retardation of brain growth
 - Late anemia and hemolysis
 - Skin malignancy
 - Delayed puberty because of long-term adverse effects on endocrines and sexual maturation.
- **Directed at nursing staff:** Headache and giddiness.

Fiberoptic Phototherapy (Bili Blankets)

An alternative phototherapy is what is termed as **fiberoptic phototherapy**. This relatively new technique employs light from a fiberoptic source which is fanned out on a cummerbund wrapped round the neonate's torso. Eye padding/shielding (covering) is not needed. Unlike the conventional phototherapy in which irradiance is maximal at the body surface nearest to the light source, irradiant energy in this technique is uniformly distributed. Further, it is simple causing no side effects. It is as effective as the conventional phototherapy. Since it is small, lightweight and portable unit, it can be used at home too. The mother can pick up the baby without discontinuing phototherapy. It, therefore, does not interfere with mother-baby bonding.

Exchange Blood Transfusion

Aims and Objectives

It is by far the best method to:

- Remove excess bilirubin and other harmful substances (say, Rh positive cells which have become noxious to

baby from blood) and to replace the blood by healthy donor blood.

- Correct severe anemia by replacing blood of low packed cell volume (PCV) by that of normal PCV. Thus, overloading of the circulation as also congestive cardiac failure are avoided.

Indications

- Any nonobstructive jaundice with serum bilirubin level of 20 mg/dL or more in fullterm and 15 mg/dL in preterm infants
- Kernicterus irrespective of serum bilirubin level
- Hemolytic disease of the newborn under the following situations:
All above, plus
 - Cord hemoglobin 10% or less
 - Cord bilirubin 5 mg/dL or more
 - Rise of serum bilirubin of more than 1mg/dL/hour. Thus, a level of 12 mg/dL within 24 hours and 15 mg/dL% within 48 hours are indications for an exchange
 - Maternal antibody titer of 1:64 or more, positive direct coombs test and previous history of a severely affected baby.

Some workers consider heart failure, reticulocyte count of 6% or more, normoblast count of 10% or more, serum bilirubin/protein ratio above 3.5 and salicylate saturation index of more than 7 as additional indications for an exchange.

Choice of Donor Blood

The donor blood should be fresh (less than 3 days old). The amount needed for an adequate exchange is about 160 mL/kg (double the blood volume). For the usual type of Rh hemolytic disease, Rh negative blood of appropriate ABO group is used. It should be crossmatched against mother's blood. Also, it should be made sure that the blood is slowly warmed to infant's temperature.

If citrated or heparinized donor blood is used, one should be prepared for hypocalcemia, hypoglycemia, hyperkalemia and metabolic acidosis. Further, citrated blood leaves the infant with relatively low hemoglobin. As a precaution, some authorities like to give injections of calcium gluconate at regular interval when using citrated blood for exchange.

Warning Signs during Exchange

These include vomiting and crying, grunting respiration and cyanosis, CCF, sudden cardiac arrest, hypothermia, hyperkalemia, hypocalcemia, acidosis, thromboembolism, arrhythmias, seizures and bleeding.

Delayed Complications

While considering the late problems that may arise from exchange transfusion, the following points should be particularly noted:

- **Anemia** of some degree is almost always seen in babies who receive exchange for hemolytic disease. The hemoglobin should, therefore be estimated every week during the first month and then every fortnightly. The hemo-

globin of less than 7 g % during first 2 or 3 weeks may be an indication for a small top-up transfusion. Iron and folic acid may be indicated if the hemoglobin fails to rise by the age of 6 weeks.

- **Sepsis**, which manifests about 12–24 hours after exchange. Fever, profuse sweating, feeding difficulty, skin rash, progressive pallor and even hepatosplenomegaly may be seen.
- **Portal thrombosis**, generally due to sepsis (at times undetected) may manifest as progressive increase in the size of spleen and bleeding from anastomotic sites.
- **Intestinal perforation** may manifest in the form of rectal bleeding, refusal to feed, bile-stained vomitus and abdominal distention. After confirming the diagnosis by X-ray studies, a laparotomy is immediately required.

Pharmacotherapy and Other Therapeutic Modalities

- **Phenobarbital**: Administering phenobarbital, 30–120 mg/day to mothers a few weeks prior to delivery or 5–8 mg/kg/day to the newborn, enhances the activity of the enzyme, glucuronyl transferase. The baby is thus, better prepared to deal with the load of bilirubin liberated after birth.

The role of phenobarbital is, therefore, more or less prophylactic. There is no point in giving phenobarbital to an infant who is already jaundiced (it will take 3–7 days and even more in preterms to demonstrate its usefulness and also cause side effects such as drowsiness, lethargy and poor feeding), except in Crigler-Najjar syndrome type II and inspissated bile with conjugated hyperbilirubinemia in which it may help by enhancing canalicular bile flow.

- **Metalloporphyrins**: In selected fullterm neonates with severe hyperbilirubinemia, a single dose of Sn-mesoporphyrin may control hyperbilirubinemia and eliminate the need for phototherapy. The beneficial effect is supposed to be related to inhibition of the activity of hemeoxygenase and reduction in the bilirubin production.
- **Other agents**: Bilirubin binding agents in the gut like agar and charcoal as also IV albumin infusion as such are of doubtful clinical value in effectively treating pathologic hyperbilirubinemia. Frequent breastfeeding cuts down enterhepatic circulation by resorption of unconjugated bilirubin from the gut.

NEONATAL CHOLESTASIS SYNDROME

The term, cholestasis (chole meaning bile, stasis meaning stoppage), denotes decrease or absence of bile flow into the duodenum so that there is a retention in blood of all the substances that are normally excreted in the bile. It may result from:

- Failure of hepatocytes to secrete bile

- Obstruction/disappearance of intrahepatic bile duct
- Obstruction of extrahepatic bile duct.

The term, neonatal cholestasis syndrome, should be restricted to conjugated hyperbilirubinemia persisting beyond a fortnight. The two most important causes are **neonatal hepatitis syndrome** (discussed later in this very chapter) and **extrahepatic biliary atresia**. See Chapter 46 (Pediatric Surgery). The topic is discussed in details in Chapter 30 (Pediatric Hepatology and Pancreatology).

G6PD DEFICIENCY

The enzyme glucose-6-phosphate dehydrogenase (G6PD) is essential for maintaining the stability of the red cell membrane. Recent times have seen increasing recognition of its genetic deficiency in various ethnic groups. This etiologic factor has, as a result, emerged as a leading cause of pathologic jaundice in the neonatal period, especially among the Mediterranean, African, Chinese and Indian stock.

It is inherited as an X-linked recessive disease. Males suffer more than females though female carriers may also manifest mild disease. For details, See Chapter 32 (Pediatric Hematology).

NEONATAL HEPATITIS SYNDROME

Neonatal hepatitis, or the so-called **giant-cell hepatitis**, may manifest any time during the first six weeks of life. Males show higher incidence. Familial and higher occurrence in siblings has also been recorded.

Etiopathogenesis

A variety of viruses, including the Australia antigen, have been incriminated.* There is evidence that the virus crosses the placenta. Multinucleated giant cells with complete loss of normal pattern of hepatic lobules and increased fibrous tissue around necrotic liver cells as also in the portal tracts are the characteristic histologic findings. Extrahepatic bile ducts are normal.

Clinical Features

The onset is usually insidious with:

- Marked jaundice (obstructive)
- Grossly enlarged liver (surface is smooth, but consistency firm)
- Moderate hepatosplenomegaly (Fig. 17.54).

Child shows poor weight gain. Vomiting is common. Activity may be normal or slow. Stools are light-colored (not typically clay-colored). Urine is high colored.

Diagnosis

Liver function tests are grossly abnormal. Liver biopsy is a must for exact diagnosis. At times, operative biopsy may be warranted. Differential diagnosis is mainly from extrahepatic biliary atresia (Table 17.14).

* Giant-cell hepatitis has also been described in nonviral diseases, e.g. galactosemia, α -1-antitrypsin deficiency, cystic fibrosis, Rotor syndrome, syphilis, toxoplasmosis, septicemia, etc.



Fig. 17.54: Neonatal hepatitis.

Treatment

Supportive therapy is the mainstay of treatment. Steroids are of doubtful value.

Prognosis

At least 25% cases of neonatal hepatitis die. Among the survivors, incidence of postnecrotic cirrhosis and portal hypertension in later years is fairly high.

HEMOLYTIC DISEASE OF THE NEWBORN

This disease is caused by incompatibility between mother’s blood group and that of the baby. Crossing over of the red cells of the fetus produces antibodies in the mother. Nothing happens to the mother. However, when these antibodies cross the placenta and enter baby’s circulation, they cause hemolysis. The resultant anemia, jaundice and other manifestations vary with the intensity of hemolysis.

- Two types of incompatibilities have been described:
1. Rh incompatibility and
 2. ABO incompatibility.

Rhesus Hemolytic Disease

(Rh Isoimmunization)

About 1 in 5 mothers with Rh negative blood group have trouble with their babies. The problem arises when the mother is carrying Rh positive baby. Among the Rh factors, D is the one almost always involved.* The first baby is rarely affected.**

Clinical Features

Clinically, Rh hemolytic disease may manifest as hydrops fetalis, icterus gravis or hemolytic anemia.

- **Hydrops fetalis:** This is the most severe form of the disease. The infant is often preterm and may die in utero or shortly after birth from severe anemia and CCF. He is markedly edematous with effusion in serous cavities (Fig. 17.55) and has gross hepatosplenomegaly. In case of stillbirth, the fetus may be macerated. Placenta is always large and edematous.
- **Icterus gravis:** When hemolysis in utero is less intense, deep jaundice appears during the first 12–24 hours. Progressive anemia and hepatosplenomegaly are invariably present. Some may have purpura. Incidence of kernicterus is high. Those who manage to survive are often left with sequelae.

Conditions in which an Rh negative mother may give birth to neonates without icterus are:

- When father too is Rh negative
- When father is heterozygous Rh positive in which case there is 25% chance of an Rh negative neonate.
- When ABO incompatibility accompanies Rh incompatibility.
- When mother is nonreactor in which case she is unable to respond by producing antibodies.

Table 17.14: Neonatal hepatitis vs biliary atresia

Features	Neonatal hepatitis	Biliary atresia
Sex	Predominantly in males	Predominantly in females
Onset	Any time during first 6 weeks of life	Around 7th day
Jaundice	Peak → moderate → mild	Mild → moderate → peak
Activity	Normal or slow	Normal
Hepatosplenomegaly	Early	Late
Liver function tests	Grossly abnormal (except alkaline phosphatase)	Slightly abnormal (except alkaline phosphatase)
Rose-Bengal test (excretion in stools)	Less than 15%	Less than 10%
Biopsy	Giant cells	Dilatation and hyperplasia of bile canaliculi
Cholangiogram	Normal	Reveals block
Australia antigen	May be present	Absent

* The various Rh factors are c, d, e, C, D and E.

** The first baby may be affected if the mother had an abortion or blood transfusion with Rh positive blood.



Fig. 17.55: Hydrops fetalis. Virtually incompatible with life, it is characterized by anasarca with fluid in serous cavities and gross hepatosplenomegaly.

- **Congenital hemolytic anemia:** This is the mildest, but also the rarest form of Rh hemolytic disease. Jaundice is generally absent. Anemia and hepatosplenomegaly are often detected towards the end of the first week or later.

Diagnosis

The diagnosis has to be made in the fetus or immediately after birth if serious consequences of the disease are to be prevented. The foremost investigation is to demonstrate that the mother is Rh negative whereas the infant is Rh positive. Occasionally, an Rh positive infant may type as Rh negative because of the **blocking antibodies**. If possible, father's Rh group should also be tested.

Direct coombs test on infant's red cells is positive. Anti-Rh titer of mother is high. Other investigations show high serum bilirubin (indirect or unconjugated), reticulocytosis, anemia, anti-Rh agglutinins and hypoglycemia.

For diagnosis of the fetus at serious risk, amniocentesis may be performed by abdominal puncture and a small amount of fluid obtained for spectrophotometric analysis. An elevated peak at 450 milli M after 24 weeks of gestation is an indication for intrauterine transfusion.

Treatment

- Surgical induction of labor during 38th week should be done when hemolytic disease is anticipated from high titer of Rh antibodies.
- After birth, specific treatment consists of giving exchange transfusion, using group "O" Rh negative blood. Exchange transfusion prevents CCF and kernicterus. It has reduced the death rate to mere 3% in infants who are born alive.
- Digitalization for CCF, thoracentesis and paracentesis for massive fluid in serous cavities and diuretics are some of the other measures of value.

Prevention

Every Rh negative mother who has given birth to an Rh positive baby should be given 1 mL of anti-D immunoglobulin IM within 72 hours of delivery. It is also indicated when:

- Rh positive blood is accidentally transfused to a Rh negative mother
- Rh negative mother who had an abortion.

This destroys or coats the Rh positive cells that have managed to enter the mother's blood and thus prevents formation of antibodies. The results of these injections are exceedingly rewarding as far as prevention of isoimmunization is concerned.

ABO-Hemolytic Disease

Unlike Rh hemolytic disease, it is generally mild. In this case, mother's group is O and infant's A or B. Likewise, she develops anti-A or anti-B antibodies in her blood. First borns are more likely to have this disease.

Clinical features may include jaundice, anemia and hepatosplenomegaly. Jaundice is frequently delayed until 48–72 hours. Peripheral blood film shows microspherocytosis. No treatment is needed in majority of the cases. If serum bilirubin exceeds 20 mg%, exchange transfusion is indicated.

KERNICTERUS

(Bilirubin Toxicity, Bilirubin Encephalopathy)

Definition

Kernicterus is defined as a bilirubin-induced brain dysfunction as a result of the deposit of bile pigments in the nuclei of the brain and spinal cord and by degeneration of nerve cells that occurs usually in infants as a part of the syndrome of erythroblastosis fetalis.

Pathophysiology

Unconjugated (indirect) bilirubin is neurotoxic, especially to basal ganglia in fullterm neonates and to cranial nerve nuclei and thalamus in preterm neonates with birth weight less than 1500 g. Hyperbilirubinemia with indirect bilirubin of 20 mg% or more, irrespective of the causative factor, can produce neurologic signs and symptoms in a newborn. In case of a preterm and/or LBW infant, kernicterus may result from a lower level of bilirubin. The basal ganglia and other nuclear areas of the brain are the predominant sites of involvement.

The term, **transient bilirubin encephalopathy**, is reserved for early bilirubin-induced neurologic dysfunction, which is temporary and reversible.

Etiology

The most common cause is the hemolytic disease of the newborn. However, conditions like Crigler-Najjar syndrome (congenital glucuronyl-transferase deficiency) can occasionally lead to this complication. Predisposing or risk factors include pre or postmaturity, VLBW, asphyxia, acidosis, hyperosmolality, sepsis as such or with meningitis, hypoalbuminemia, hypothermia, hypercarbia and rapid rate of rise of serum bilirubin.

Clinical Features

Manifestation of transient bilirubin encephalopathy is increasing lethargy with rising serum bilirubin level. Manifestations may be categorized into four stages (Box 17.32).

Box 17.32**Staging of kernicterus (bilirubin encephalopathy)**

- **Stage I:** Poor feeding, lethargy, vomiting, high-pitched cry, poor Moro reflex and poor tone.
- **Stage II:** Fever, seizures, rigidity, opisthotonos, oculogyric crisis, paralysis of upward gaze and even death.
- **Stage III:** Reduction in spasticity.
- **Stage IV:** This is the stage of long-term sequelae in the form of spasticity, athetosis, deafness, mental retardation, dental dysplasia and paralysis of upward gaze, etc. (cerebral palsy).

Investigations

These include:

- Serum bilirubin, bilirubin binding tests
- BAER
- High speed computer technology for cry analysis
- Pulsed nuclear magnetic resonance (PNMR) spectroscopy and
- Brazelton neonatal behavioral assessment scale (BNBAS).

Treatment

A prompt exchange transfusion leads to recovery in transient bilirubin encephalopathy. Results in stages II and III are equivocal.

Prognosis

Those who manage to survive are left with sequelae of extrapyramidal involvement, deafness and mental retardation, etc.

NEONATAL SEIZURES

Neonatal seizures constitute a common neonatal emergency, especially in preterm and LBW babies in whom the incidence is many fold compared to the fullterm healthy babies.

Etiology

Neonatal seizures are usually secondary to HIE, hypocalcemia, hypoglycemia or septicemia with meningitis (Box 17.33). For etiology of neonatal convulsions according to the time of onset, See Chapter 28 (Pediatric Neurology). These are never febrile or idiopathic.

Clinical Features

- Clinically, 5 major types of seizures are seen in neonates, namely:
 1. Subtle
 2. Generalized tonic
 3. Multifocal clonic
 4. Focal clonic and
 5. Myoclonic.
- About 50% of all neonatal seizures are subtle which may manifest as eye movements (blinking, fluttering, deviation with jerking, eye opening sustained with ocular fixation), orobucolingual movements, screening, rowing and pedalling movements and apneic spells.

Box 17.33**Etiology of neonatal seizures**

- **Developmental neurologic problems:** Congenital hydrocephalus, microcephaly, cerebral dysgenesis, porencephaly, polymicrogyria, pachygyria, hydranencephaly, lissencephaly and agenesis of corpus callosum.
- **Perinatal complications** HIE, birth asphyxia, birth injuries (especially with CNS involvement), intracranial bleed (IVH, SAH).
- **Perinatal infections** Meningitis, septicemia, intrauterine infections (TORCH).
- **Metabolic problems** Hypocalcemia, hypoglycemia, hypomagnesemia, hypo or hypernatremia, pyridoxine dependency, severe hyperbilirubinemia with kernicterus (bilirubin encephalopathy), inborn errors of metabolism (amino acid metabolism, organic acidemias).
- **Drugs** Neonates born to mothers with narcotic addiction (narcotic withdrawal syndrome), theophylline, propylene glycol, in advertent injection of local anesthesia.
- **Idiopathic.**

Abbreviations: CNS, central nervous system; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage; HIE, hypoxic-ischemic encephalopathy; TORCH, syphilis, toxoplasma, other agents, rubella, cytomegalovirus and herpes simplex.

- Pure tonic and clonic seizures are not seen in neonates since neonatal seizures are by and large subcortical in origin.
- Twitching, rolling of the eyes, generalized tonic stiffness without clonic phase but with apnea, or sudden irregularity of respiration or only a change in color with vacant look may reflect a convulsive disorder.

Investigations

Investigations should include:

- Blood for calcium, phosphorus and sugar
- Lumbar puncture (LP)
- Electroencephalogram (EEG) in the interictal period. A normal EEG does not rule out seizure activity
- Ultrasonography and CT scan in some cases.

Treatment

Major steps of treatment are:

- Stabilization of vitals airway, breathing, circulation (ABC)
- Correction of metabolic abnormalities such as hypoglycemia and hypocalcemia
- Anticonvulsant therapy.

Phenobarbital 20 mg/kg (IV) slowly over 10 minutes followed by, in case of no response, two doses, each 10 mg/kg, at 15 minutes interval. Total dose should not exceed 40 mg/kg. Maintenance dose is 5 mg/kg once a day. If no response, phenytoin, 20 mg/kg (IV) slowly over 20 minutes (loading). Maintenance dose is 5 mg/kg once a day.

For intractable seizures, lorazepam, midazolam, clonazepam, valproate, paraldehyde, magnesium sulfate and even lignocaine may be employed (Box 17.34).

If the cause is not traceable and the response to anticonvulsants and/or correction of biochemical or metabolic defect is unsatisfactory, it is advisable to give a therapeutic trial with pyridoxine, 50–100 mg, calcium gluconate, 5–10 mL of 10%

Box 17.34 Drugs for acute neonatal seizures

Phenobarbital	10–20 mg/kg/dose (IV) (Gold standard), 5 mg/kg/day (IV, O) as maintenance
Phenytoin	10–20 mg/kg/dose (IV), 5 mg/kg/day (IV, O) as maintenance
Paraldehyde	0.15 mL/kg/dose (IM)
Lorazepam	0.05 mg/kg/dose (IV)
Diazepam	0.5 mg/kg/dose (IV). (best avoided)

Abbreviations: IV, intravenous; IM, intramuscular; O, orally.

solution, by slow IV injection and 1–2 mL/kg of 50% glucose, diluted with distilled water. An infrequent, brief, simple, mild seizure that does not interfere with cardiorespiratory status need not be considered as an evidence of poor response.

The pediatrician may well reverse the order of anti-convulsant therapy and pyridoxine/calcium gluconate therapy depending on the merits of the case. Unless there is an indication for long-term therapy, an anticonvulsant agent is continued for only 4–12 weeks following control of convulsions and then slowly withdrawn.

Prognosis

The best prognosis is in hypocalcemic seizures. Neonatal seizures secondary to birth trauma and hypoxia show bad outcome with almost 40% mortality in the neonatal period per se. Of the survivors, 25% suffer from recurrent seizures and neurodevelopmental defects.

METABOLIC DISORDERS OF THE NEWBORN

Neonatal Hypoglycemia

Definition

When blood glucose falls under 40 mg/dL, regardless of the gestational age of the neonate, hypoglycemia is said to be present. Its incidence, including both symptomatic and asymptomatic cases is approximately 20% in fullterm and 50% in preterm/LBW babies.

Etiology/Predisposing Factors

Predisposing conditions include IUGR, prematurity, infants of diabetic mother (IDM), infants of toxemic mothers and smaller of the twins in case of transient hypoglycemia and, Rh incompatibility, prolonged hypoxia, hypothermia, septicemia, metabolic disorders like galactosemia, glycogen-storage disease, maple syrup urine disease or fructosemia, hyperinsulin states (leucine sensitivity, beta cell adenoma) exchange transfusion with acid-citrate-dextrose (ACD) blood, etc. in case of persistent hypoglycemia.

The modus operandi of development of symptoms is release of epinephrine and activation of autonomic nervous system plus reduced utilization of glucose in the cerebrum.

Clinical Features

Clinical manifestations in symptomatic hypoglycemia include sweating, lethargy, irritability, jitteriness, tachycardia, tremors, cyanosis and apneic spells and seizures.

Treatment

- Treatment in symptomatic neonates consists of giving a bolus dose of 10% dextrose, 2 mL/kg (IV), i.e. 200 mg/kg. In case of coexisting seizures, 4 mL/kg of 25% dextrose (IV) should be the choice. This needs to be followed by IV dextrose, 4–10 mg/kg/minute until the blood sugar rises >40 mg/dL.
- Prednisolone, 1–2 mg/kg/day (O) or hydrocortisone, 5 mg/kg, every 12 hours, is indicated if hypoglycemia remains unresponsive after 12–24 hours of IV drip.
- Glucagon, 300 mg/kg, IM or IV, (as such or in combination with epinephrine 1 in 10,000, 0.1–0.3 mL/kg IV, IM or SC) is indicated in hypoglycemia associated with maternal diabetes or Rh incompatibility.
- Diazoxide, 25 mg/kg/day (IV, IM) in 3–4 divided doses is of particular value in intractable hypoglycemia in IDM.

Prevention

Initiating the neonate on breastfeeding within half an hour of birth and prevention of prematurity and LBW are important preventive strategies.

Prognosis

Neonatal hypoglycemia, if not controlled, may prove fatal. Some 50% of LBW and IDM survivors may show evidence of cerebral palsy, epilepsy or mental retardation.

NEONATAL HYPOCALCEMIA

(Neonatal Tetany)

Newborns on cow milk formula (which is known to be rich in phosphates) may suffer from tetany. The condition is not uncommon.

Etiology

Predisposing factors include LBW, delayed feeding, maternal diabetes mellitus, difficult and prolonged labor, emergency cesarean section and other complications associated with delivery, APH, toxemias, electrolyte disturbances (acidosis), congenital rickets, exchange transfusion with citrate blood, renal disorders, hypoproteinemia, idiopathic hypoparathyroidism and maternal hypoparathyroidism (DiGeorge syndrome).

Clinical Features

Clinical manifestations include tremors, twitching, jitteriness, frank seizures (towards end of first week of life) and, infrequently, laryngeal spasm and carpopedal spasm. The baby remains all right in between the attacks.

Chvostek sign, a normal finding in a neonate, is not of value. Association of tetany with intractable thrush (moniliosis) and failure to thrive must invite attention to the possibility of DiGeorge syndrome or thymic hypoplasia. See Chapter 34 (Pediatric Immunology).

Investigations

- Serum calcium is reduced, almost always below 8 mg/dL.

- 318** ■ Serum phosphate is, however, high.
- ECG shows prolonged QTc interval.
 - In selected situations, chest X-ray is helpful to exclude thymic hypoplasia or aplasia.

Treatment

Treatment consists of administering 5–10 mL (2 mL/kg) of 10% calcium gluconate, very slowly, by IV route. Response is dramatic. Later, the baby should be put on maintenance oral calcium gluconate, 2–3 g/day in a 10% solution in divided doses, for several weeks. If the baby had been on cow milk, he should be shifted to mother's milk.

If response to calcium therapy is poor, the infant should be administered intramuscular magnesium sulfate (vide infra).

NEONATAL HYPOMAGNESEMIA

When serum magnesium levels fall under 1.5 mg/dL (0.62 mmol/L), biochemical hypomagnesemia is said to be present. However, clinical manifestations of hypomagnesemia usually develop when the levels fall under 1.2 mg/dL.

- Etiologic factors include inadequate placental transfer, poor intestinal absorption, hypoparathyroidism, hyperphosphatemia, renal loss, defective magnesium and calcium homeostasis, exchange transfusion, total parenteral nutrition (TPN) and IDM. Occasionally, it may coexist with hypocalcemia.
- Manifestations are indistinguishable from those seen in hypocalcemia and tetany. Perhaps, hypomagnesemia causes symptoms through accompanying hypocalcemia.
- In the diagnosis, the most vital clue is hypocalcemic seizures/tetany not responding to adequate calcium therapy.
- Treatment comprises of immediate administration of magnesium sulfate, 0.25 mL/kg of a 50% solution, IM. Usually a 1–2 week therapy in the same dose (IM, O) suffices.

INFANTS OF DIABETIC MOTHERS

Maternal diabetes may cause fetal death in third trimester of pregnancy.

Clinical Features

Newborns of diabetic mothers, who themselves may have suffered from toxemia of pregnancy and hydramnios are usually remarkably heavy, plump, full-faced (macrosomia), plethoric and covered with lot of vernix caseosa. Mortality, both in utero and neonatal life, is relatively high.

Such infants are prone to develop hypoglycemia, hypocalcemia, idiopathic respiratory distress syndrome, hyperbilirubinemia, polycythemia, persistent pulmonary hypertension, cardiomyopathy, lazy left colon syndrome, renal and adrenal vein thrombosis and congenital malformations, including those of skeleton, heart and respiratory system. Hypertrichosis and hairy pinna are striking signs.

Treatment

Unlike in the past, it is a practice nowadays to allow the pregnancy to reach closer to term while a good antenatal check-up is maintained on fetal growth and the attending obstetrician ensures control of maternal diabetes.

The infant is treated in the same way as a preterm or light for dates, preferably in an incubator. It is helpful to administer 10% glucose at a rate of 10 mL/hour. Oral feeding should be introduced at 12 hours or as early as possible if there is respiratory distress.

Prognosis

Only 1–2% of such babies may end up with diabetes mellitus in childhood.

TRANSPORT OF THE SICK NEONATES

Types

The followings types of neonatal transport are usually required:

- From village level to level I center
- From level I to level II center
- From level II to level III center
- From labor room to nursery with level II or III facilities
- From neonatal intensive care unit (NICU) to operation theater.

Indications

- **In utero transport:** Box 17.35 gives indications of in utero transport if the birth of an at risk neonate is anticipated.
- **Postnatal transport:** Box 17.36 gives the list of danger signs of a sick neonate that should guide the health workers to transport the neonate to an institution. Table 17.15 gives the indications for transport of sick neonates to NICU.

Major Principles

- Ensuring that full justification for transport exists and explaining it to the parents/attendants
- Ensuring communication of arrival of the sick baby to the referral center and providing all the case record to the attendants for the benefit of the referral center.

Box 17.35 Indications of in utero transport/referral

- Onset of premature labor in a pregnancy of 33 weeks or less
- Multiple pregnancy or abnormal presentation
- Antepartum hemorrhage and pre-eclampsia
- Cephalopelvic disproportion
- Prolonged rupture of membranes, especially in the presence of maternal infection
- Serious maternal cardiovascular or renal disorders
- Previous severe isoimmunization or other serious fetomaternal problems
- Fetal anomalies like diaphragmatic hernia or tracheoesophageal fistula
- IUGR, especially with oligohydramnios.

Abbreviation: IUGR, intrauterine growth retardation.

Box 17.36**Danger signs that indicate transport from the community to the institution with at least level II facilities**

- Poor sucking
- Rapid or difficult breathing with a rate (>60/minute) and/or indrawing of chest spaces
- Cold clammy or too warm skin
- Abnormal movements including stiffness and uprolling of eyes
- Abdominal distention
- Jaundice.

Table 17.15: Indications for transport of sick neonates to NICU

Status	Absolute indication	Relative indication
LBW	Less than 1500 g	1500–200 g
Prematurity	Less than 32 weeks	32–36 weeks
Respiratory distress	Moderate to severe, not improving with oxygen, airway obstruction, apnea	Mild respiratory distress
Fulminant infection	Septicemia Meningitis Pneumonia Tetanus	
Shock	Hypotension Oliguria	
Birth asphyxia	HIE	Congenital heart disease
Congenital malformations	Diaphragmatic hernia, TEF, Intestinal obstruction, Congenital heart disease, (Symptomatic acyanotic and all cyanotic)	(asymptomatic) Gastroschisis
Miscellaneous	Severe hyperbilirubinemia Birth trauma	IDM Neonatal seizures, Coagulopathy, Genetic/metabolic disorders

Abbreviations: NICU, neonatal intensive care unit; LBW, low birth weight; TEF, tracheoesophageal fistula; HIE, hypoxic-ischemic encephalopathy; IDM, infants of diabetic mothers.

- Before transporting the neonate, ensuring that he is stabilized as far as possible, especially in regards to his hypothermia.
- Ensuring warmth (thermal stability) for the neonate during transport. The most practical method in developing countries is keeping the neonate close to the mother's chest, making available the skin to skin contact.
- Providing instructions and guidelines to the attendants for care during transport. In case of an IV line, the attendants should know about the number of drops/minute as also the technique of changing the bottle.
- The reverse transport should also be communicated to the referring unit, say from NICU to postnatal wards or back to the community health center.

MATERNAL MEDICATION AND ADVERSE EFFECTS ON THE FETUS

As a rule, all medications to the pregnant mother should be avoided unless and until the attending doctor finds that the benefits of a particular medicine outweighs its

Table 17.16: Maternal medication and adverse effects on fetus

Drugs	Adverse effects (teratogenic)
Diazepam	Cleft lip, cleft palate, hypothermia, apnea
Quinine	Deafness, thrombocytopenia, neurologic anomalies
Chloroquine (prolonged use)	Deafness
Sulfas	Hyperbilirubinemia
Streptomycin	Eighth nerve deafness, renal damage
Tetracyclines	Deposition in teeth, staining of teeth, enamel hypoplasia, retardation of bone growth, congenital cataracts
Propranolol	Growth retardation, thrombocytopenia
Indomethacin	LBW, platelet dysfunction
Heroin	Intrauterine death, LBW, SIDS
Phenobarbital	Cleft lip, cleft palate, CHD, respiratory depression, withdrawal symptoms
Phenytoin*	Various malformations in relation to limbs, heart and face
Valproate	Facial anomalies, spina bifida and developmental delay
Smoking	LBW, abnormal placentation
Alcoholism	IUGR, mental retardation, microcephaly, CHD flexion contractures
Diethylstilbesterol or Progestrogen	Genitourinary anomalies in males, adenosis, carcinoma of vagina in females Masculinization of female fetus with testosterone
Iodides (in third trimester)	Congenital goiter, hypothyroidism
Cyclophosphamide	Multiple deformities
Progesterone (in third trimester)	Malformations of external genitalia, postpubertal vaginal adenocarcinoma
Sulfonurea (third trimester)	Neonatal hypoglycemia, brain damage
Thalidomide (third trimester)	Limb deformities, defects of CVS, ears and eyes
Radiation	Mental retardation, microcephaly

* Amongst antiepileptic drugs (AEDs), the most teratogenic are phenytoin, valproate and trimethadione. The safest are carbamazepine, phenobarbital and primidone.

Abbreviations: LBW, low birth weight; SIDS, sudden infant death syndrome; CHD, congenital heart disease; IUGR, intrauterine growth retardation/restriction; CVS, cardiovascular system.

risks to the fetus (Table 17.16). The risk of teratogenic effect is most pronounced during embryogenesis. In later pregnancy, the adverse effects are in the form of disturbance of enzyme system or organ dysfunction.

MATERNAL MEDICATION AND ADVERSE EFFECTS ON BREASTFED INFANT

Table 17.17 lists the adverse effects of medication on breastfed infants.

Table 17.17: Adverse effects of maternal medication on breastfed infants

Drug/agent	Adverse effect
Antithyroids	Hypothyroidism
Phenobarbital	Drowsiness, rickets, drug rash, methemoglobinemia
Phenytoin	Rickets, drug rash, methemoglobinemia
Diazepam	Drowsiness, rise in serum bilirubin
Laxatives	Loose motions
Penicillin	Rash
Narcotics	Withdrawal symptoms
Theophylline	Irritability
Lithium	Hypotonia
Sulfas	Drug rash, hemolysis
Salicylates	Drug rash, interference in platelet function
Oral contraceptives	FTT, gynecomastia

Abbreviation: FTT, failure to thrive.

Table 17.18: Food and environmental agents having adverse effect(s) on the infant and/or lactation

Food/environmental agent	Adverse effect (s)
Chocolates	Irritability, diarrhea (if the mother consumes >16 oz/day)
Fava beans	Hemolytic anemia in G6PD deficiency
Absolute vegetarianism	Vitamin B ₁₂ deficiency
Hexachlorobenzene	Rash, diarrhea, vomiting, dark discoloration of urine, neurotoxicity
Lead	Neurotoxicity
Mercury	Retarded neurodevelopment
Tetrachloroethylene	Dark discoloration of urine, obstructive jaundice

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.

FOOD AND ENVIRONMENTAL AGENTS AND ADVERSE EFFECTS ON THE INFANT

These are summarized in Table 17.18.

MATERNAL DISEASE AND THE GROWING FETUS AND THE NEWBORN

Maternal HIV/AIDS

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in mother may be transmitted to the infant during pregnancy, during birth or via breastfeeding; the so-called **mother to child transmission** (MTCT). The overall risk of such transmission is 20–45%. In nonbreastfed infants, it is 15–30% since breastfeeding as such is responsible for 5–20 % risk.

Interventions aimed at cutting down this risk include:

- Antiretroviral therapy (ART) prophylaxis during pregnancy and labor and to the baby in first 6 weeks of life
- Elective cesarean section before onset of labor and before rupture of membranes

Box 17.37

Recommendations of ART during pregnancy and for the infant

For mother

- ART indicated for mother
 - Triple drug ART: AZT + 3TC + NVP/EVF
- ART to prevent perinatal transmission
 - Option 1: Triple ART at 14 week of gestation until 1 week after exposure to breast milk has stopped.
 - Option 2: Antepartum AZT at 14 week + intrapartum single dose NVP + AZT + 3TC + postpartum AZT + 3TC for 7 days

For infant

- If mother got triple drug ART during pregnancy and breastfeeding phase—NVP or AZT × 6 weeks
- If mother got only AZT for ART
- Breastfed—daily NVP × 1 week from birth
- Nonbreastfed—NVP or AZT × 6 weeks.

Abbreviations: ART, antiretroviral therapy; AZT, azidothymidine; NVP, Nevirapine; EVF, efavirenz; 3TC, Lamivudine.

- No breastfeeding when parents can afford artificial feeding. Box 17.37 summarizes recommendations for ART.

If feasible, mothers with HIV/AIDS should withhold breastfeeding and, instead give replacement feeding in the form of commercial formula milk. In case replacement feeding is not feasible, mother should give exclusive breastfeeding for 6 months.

Maternal Hepatitis B Infection

Infants of mothers with hepatitis B infection need to get hepatitis B vaccine within 12 hours of birth and, if feasible, hepatitis B immunoglobulin (HBIG), 200 IU (0.5 mL) IM again within 12 hours of birth for enhanced protection. The two injections should be given using separate syringes and at different sites. With just the vaccine, protection is 70–75%. When both vaccine and HBIG, protection shoots to 85–95%.

Maternal Tuberculosis

If the mother suffers from active tuberculosis, the infant needs to be offered protection from acquisition of infection with isoniazid (INH) × 6 months followed 2 weeks later with BCG vaccine. Meanwhile, if the evaluation at 6 weeks shows evidence of tuberculosis, solitary INH should be replaced by full antituberculous therapy (ATT).

Maternal Syphilis

Maternal syphilis that remains inadequately treated is an indication for treatment of the infant with penicillin (procaine or benzathine) in addition to treatment of the mother as well as the father.

Maternal Hypothyroidism

Neonates born to mothers not receiving or receiving only inadequate replacement thyroxine therapy need to be screened for hypothyroidism. Such screening can be done on cord blood or blood sample taken after 72 hours of birth.

Box 17.38 Adverse effects of maternal diabetes on fetus

- Fetal death in last trimester
- Large fetal size (macrosomia)
- Hypoglycemia
- Hypocalcemia
- Hyperbilirubinemia
- Polycythemia
- Enhanced risk of congenital malformations, including cardiovascular anomalies.

Maternal Diabetes

Diabetes in the mother, especially poorly controlled/uncontrolled, is likely to have adverse effects on the fetus as well as the infant after delivery (Box 17.38).

- During pregnancy, high blood sugar affects the fetus in the form of hyperglycemia and, as a consequence, hyperinsulinemia which is responsible for large fetal size from excessive synthesis of protein, lipids and glycogen.
- After birth, hyperinsulinemia results in hypoglycemia, often accompanied by hypocalcemia and hyperbilirubinemia and surfactant deficiency which predispose the infant to RDS.

HIGH-RISK NEONATES (HRN)**Definition**

By high-risk neonate is meant a neonate who is likely to develop complications resulting in morbidity (growth/development failure, neurodevelopmental disability) and even death as a result of prenatal (including preconceptional), fetal, natal or postnatal factors. Such a neonate needs to be under expert observation and care

Etiology

High-risk neonates may have conditions involving the fetus, during birth or soon after birth (Box 17.39).

Identification

In order to cut down neonatal morbidity and mortality, it is important to identify neonates at risk at the earliest. Table 17.19 lists the observations on placenta, cord and membranes pointing to HRN.

Care/Therapeutic Considerations

A group of HRNs need only good observation and initial vigilance. Yet, a proportion of the HRNs may need NICU management. Today, with greater sensitization on the part of the care-providers and improved antenatal, perinatal and neonatal care, many premature, VLBW and ELBV neonates survive. However, they run the risk of long-term morbidities, including failure to thrive, neuro developmental delay, visual and hearing handicaps, etc. These infants need a good follow-up in order to prevent, detect and manage these disabilities.

Box 17.39 Conditions/factors related to high-risk neonate**Preconceptional**

- Genetic predisposition
- Maternal age (<16 or >40 years)
- Substance abuse
- Maternal diseases: Diabetes, hypertension, SLE
- Consanguinity

Pregnancy

- Prematurity <37 weeks
- Postmaturity >42 weeks
- LBW
- Congenital malformations
- PROM
- Meconium aspiration

Natal

- HIE/asphyxia

Postnatal

- BPD
- PPHN
- RDS
- Congenital infections–STORCH/TORCH
- Sepsis
- Pathologic jaundice.

Abbreviations: SLE, systemic lupus erythematosus; STORCH, syphilis, toxoplasma, other agents, rubella, cytomegalovirus and herpes simplex; TORCH, toxoplasma, other agents, rubella, cytomegalovirus and herpes simplex; LBW, low birth weight; PROM, Prolonged rupture of membranes; HIE, hypoxic-ischemic encephalopathy; RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; PPHN, persistent pulmonary hypertension of the newborn

Table 17.19: Observations on placenta, cord and membranes pointing to HRN in identifying HRNs

Observation	Inference
Placental pallor, retroplacental hematoma, tears in succenturiate lobes	Fetal blood loss
Placental edema	Fetofetal transfusion syndrome, hydrops fetalis, congenital nephrosis, hepatic disease
Granules on the amnion (amnion nodosum)	Pulmonary hypoplasia, renal agenesis
Small whitish nodules on the cord	Candida infection
Oligohydramnios	Pulmonary hypoplasia, renal agenesis
Short cords, non-coiled cords	Chromosomal defects, omphalocele
True umbilical cord knots	Long cord, small fetal size, polyhydramnios, monoamniotic twinning, fetal demise, low Apgar score
Chorioangioma	Prematurity, abruption placenta, IUGR
Meconium staining	In utero stress
Opacity of fetal surface of placenta	Infection
Single umbilical arteries	Congenital renal abnormalities and syndromes

Abbreviations: IUGR, intrauterine growth retardation; HRN, high-risk neonates.

Box 17.40**Indications of follow-up in high-risk neonates****In relation to the newborn**

- Prematurity (gestation less than 32 weeks) and/or LBW (less than 1500 g)
- HIE and/or Apgar at 5 min less than 4
- Sepsis (culture positive) and/or meningitis
- Hyperbilirubinemia (TSB more than 20 mg/dL) and/or need for exchange transfusion
- Metabolic disorders: Hypoglycemia, hypocalcemia.

In relation to therapeutics

Mechanical ventilation (more than 24 hours).

Abbreviations: LBW, low birth weight; HIE, hypoxic-ischemic encephalopathy; TSB, total serum bilirubin.

Follow-up Program**Goals**

- Early identification and solutions of developmental disabilities and medical complications and ongoing medical problems/ailments
- Referral for comprehensive evaluation
- Parent counseling regarding anticipatory guidance on recognizing early signs of developmental disabilities and behavioral problems, etc.

Staff in the Neonatal Follow-up Clinic

A pediatrician with expertise in neonatology and neurodevelopment with facilities for referrals to audiologist, speech therapist, ophthalmologist, nutritionist and pediatric/orthopedic surgeon, etc.

Indications

These are listed in Box 17.40. In short, whenever a neonate requires treatment in a NICU, it is important to have good follow-up to ensure optimal quality of life.

Time Schedule/Frame The follow-up schedule is listed in Box 17.41.

Components of Follow-up Checkup

- **Growth monitoring:** Head circumference, weight, length and midarm circumference.
- **Developmental assessment:** Gross motor, fine motor, language and personal-social milestones. Age-appropriate stimulation helps in improved development.
- **Neurologic assessment:** Posture, muscle tone (extremities, neck and trunk), reflexes, any asymmetry and history of seizures.
- **Ophthalmic examination:** Cataract, squint, vision, optic atrophy; ROP at 31 weeks postmenstrual age (PMA) to 4 weeks chronologic age.
- **Ear nose and throat (ENT) examination:** BAERA for hearing loss at 40 weeks PMA to 3 months postnatal age. Hearing is essential for acquisition of language.
- **Care of ongoing problems:** Loose motions, upper respiratory tract infections (URTI) and lower respiratory tract infection (LRTI), etc.
- **Feeding:** Failure to thrive (FTT) in spite of exclusive breastfeeding, supplementation with a formula advisable.

- **Immunization:** It should be in accordance with the chronologic age and not the corrected age.

Multidisciplinary evaluation contributes to identify areas of strength to develop strategies for intervention and provide realistic data for parent counseling.

NEWBORN SCREENING**Definition**

Newborn screening, a sort of secondary prevention, is defined as a strategy that aims to prevent or mitigate the effects of a serious neonatal disease by identifying it early and treating it or even eliminating it at a nascent stage.

In most cases, blood collection after 72 hours and within 7 days of life on a filter paper is the standard method of screening newborns for most conditions, especially congenital hypothyroidism and metabolic disorders.

Diseases Needing Screening

Usually it is done to identify:

- Metabolic diseases
- Critical congenital heart diseases
- Hearing problems
- Vision problems
- Malformations
- Developmental dysplasia of hip
- Developmental disorders.

Metabolic Screening

It includes screening for metabolic disorders such as:

- Phenylketonuria
- Cystic fibrosis
- Congenital hypothyroidism
- Hemoglobinopathies
- Congenital adrenal hyperplasia
- Galactosemia
- Deficiency of biotinidase
- Medium chain acetyl CoA dehydrogenase deficiency (MCADD)
- Aminoacidopathies
- Carnitine cycle defect
- Organic aciduria
- Fatty acid oxidation.

Screening Tests

- Tandem mass spectrometry for diagnosing aminoacidopathies, carnitine cycle defect, organic acidemia and fatty acid oxidation.
- Molecular testing analysis for diagnosing diseases such as cystic fibrosis.

Critical Congenital Heart Disease

For this purpose, motion-tolerant pulse oximeter after the suspected infant is at least 24 hours of life is used. If screening turns out to be positive, diagnostic echocardiograph is warranted to confirm the diagnosis. Moreover infectious

Box 17.41**Time schedule for follow-up in high-risk neonates**

- **First check-up:** After 2 weeks of discharge
- **Second check-up:** At 6 weeks
- **Third check-up:** At 10 weeks
- **Fourth check-up:** At 14 weeks
- **Subsequent check-ups:** At 3, 6, 9, 12 and 18 months of corrected age
- **Thereafter:** Every 6 month until at least 5 years of age.

and pulmonary causes of hypoxemia are also needed to be ruled out. Notably, it requires no special expertise.

Hearing

Initial hearing screening should be done using evoked otoacoustic emissions during neonatal period, preferably 12 hours after birth. Both ears need to be screened individually. It may be done twice.

A neonate failing to pass the screening test needs a referral to a higher center for rescreening with evoked otoacoustic emissions, auditory brainstem response or a combination of both. Failing the two tests, the infant should be referred for diagnostic audiological evaluation.

Vision

This screening involves 2 areas:

1. **Red reflex:** The testing is done by holding a direct ophthalmoscope close to the examiner's eye with the ophthalmoscope lens set at "0". Ophthalmoscopic light is projected onto both eyes of the neonate simultaneously. Dark spots in the red reflex, a markedly diminished reflex, presence of white reflex or asymmetry of reflexes (Bruckner reflex) are indicators for referral to an ophthalmologist.
2. **Retinopathy of prematurity:** Neonates less than 34 weeks gestation/birth weight less than 1800 g, neonates more than 34 weeks gestation, but birth weight between 1500–2000 g, neonates requiring cardiorespiratory support are candidates for ROP screening. Follow-up examinations are also carried out as per a standard protocol.

NEONATAL HYPERBILIRUBINEMIA

Though physiological in a large majority of cases, in some, infants, neonatal hyperbilirubinemia may become severe with risk of acute bilirubin encephalopathy. It is, therefore, important to check serum bilirubin at 5–7 day when it is expected to be at peak. The AAP guidelines which are adopted virtually globally are given in Box 17.42.

Box 17.42**Universal bilirubin screening for prevention and management of hyperbilirubinemia in neonates**

- Promote and support successful breastfeeding.
- Perform a systemic assessment before discharge for the risk of severe hyperbilirubinemia.
- Provide early and focused follow-up based on risk assessment.
- As and when indicated, treat newborns with phototherapy or exchange transfusion.

Malformations

The crux of malformation screening is a routine, but detailed examination of all newborns in the first 24 hours of birth with special reference to anthropometry, dysmorphism, birth trauma, neurological examination and external anatomy, etc is a must. As a rule, detection of one malformation should prompt an evaluation for further associated anomalies.

Developmental Dysplasia

In Western countries, screening for developmental dysplasia of the hip (DDH) comprises of:

- Serial physical examinations of the hip and lower extremities employing the Barlow and Ortolani procedures.
- Ultrasonography of hip at 6 weeks of age. Since DDH is very infrequent in India, screening may be restricted to limited situations.

Developmental Screening

Neurodevelopmental abnormalities existing early in development create the potential for altered responses to environmental stimuli and for maximum impact of appropriately targeted experiences.

There is huge evidence that high-quality early interventions have positive influence on the development of the child with a disability. Neonatal screening may be useful in detecting any mental retardation and developmental disability (MRDD) at an early stage and initiate interventional steps.

COMMUNITY CARE OF THE NEWBORN**(Home-based Newborn Care)**

In India, around 33% deliveries are still conducted by untrained birth attendants. Most of these neonates fail to receive proper care with unfavorable outcome in the form of high morbidity and mortality. Home-based newborn care is, therefore, mandatory.

Objectives

- Early detection and special care of preterm and LBW neonates.
- Early identification of illness and provision of appropriate care and referral.
- Supporting the family for adoption of healthy practices and build confidence and skills of the mother to safeguard her health and that of the neonate.

Key Activities

- Care for every newborn through a series of home visits by a trained health worker—usually an Accredited Social Health Activist (ASHA) in the first 6 weeks of life (Fig. 17.56).
- Information and skills to the mother and the family of every newborn to ensure better health outcomes.
- An examination of every newborn for prematurity and LBW.



Fig. 17.56: The key health workers for community care of the newborn (home-based newborn care) in India are ASHAs.

- Extra home visits for preterm and LBW infants by ASHA or ANM and referral for appropriate care as per protocol.
- Early identification of illness in the newborn and provision of adequate care at home or referral.
- Follow-up of sick newborns after they are discharged from facilities.
- Counseling the mother on postpartum care, recognition of postpartum complications and enabling referral.
- Counseling the mother for adoption of an appropriate family planning method.

Role of ASHA

The key worker, ASHA's role in the delivery of home-based care to the community is briefed in Box 17.43.

Box 17.43

Time schedule for home visits and services offered by ASHA

Home delivery time schedule

Post-delivery day 1, 3, 7, 14, 21, 28, 42

Institutional delivery time schedule

Post-delivery day 3, 7, 14, 21, 28, 42

Services offered

- Essential care of the newborn
- Examination of the newborn
- Early recognition of danger signs, stabilization and referral
- Counseling the mother for breastfeeding, warmth and care of the baby
- Immunization
- Postpartum care
- Use of family planning methods.

Multiple Choice Questions

1. Therapeutic hypothermia for HIE is characterized by all except:
 - A. Induction phase should be rapid and usually lasts between 30–120 minutes
 - B. Maintenance phase lasts for 72 hours and should have minimal fluctuations
 - C. Rewarming phase must be rapid at rate of 0.5°C per hour
 - D. Avoidance of overcooling to below 30°C
2. Infant conditions as contraindications to breast feeding include all except:
 - A. Galactosemia
 - B. Glucose-6-phosphate dehydrogenase deficiency
 - C. Maple syrup urine disease
 - D. Phenylketonuria
3. Baby born to HBsAg positive mother hours needs all, except:
 - A. HBIG and HBV at different sites IM within 12 hours of birth
 - B. Two more doses of HBV at 6 weeks and 6 month
 - C. If HBIG not available/affordable HBV vaccine be given at 0,1,2 and additional dose at 9 month
 - D. Tested for HBsAg and HBsAg antibodies to identify carrier/non-responder at 6 weeks
4. As per NRP guidelines 2010 all of the following are true except:
 - A. First 30 seconds initial steps, if HR <100, do PPV
 - B. Second 30 seconds PPV, if HR <60, CPR
 - C. CPR given in ratio 2:1
 - D. If HR <60 after CPR, epinephrine IV
5. In management of MAS all are correct, except:
 - A. Oxygen therapy is delivered via hood box
 - B. CPAP of 4 cm H₂O should be provided if oxygen requirement exceeds 0.6
 - C. MV required for respiratory acidosis to maintain pH 7.3–7.5, PCO₂– 30–50 torr and PaO₂>100 torr
 - D. May need surfactant, HFOV, INO

contd...

6. Birth injuries commonly occurring during breech deliveries include all, except:
 - A. Bony injuries, e.g. fracture of long bones
 - B. Intracranial bleeds due to adverse forces on the dura mater
 - C. Nerve injuries, e.g. Erb palsy due to seventh cervical and eighth thoracic nerve roots
 - D. Sternomastoid tumour due to traction on neck
7. Most frequently encountered orthopedic injury in the neonate:
 - A. Humeral fracture
 - B. Clavicular fracture
 - C. Femoral fracture
 - D. Shoulder dislocation
8. The single most important risk factor for neonatal sepsis:
 - A. Premature rupture of membranes
 - B. Low birthweight
 - C. Peak intrapartum temperature
 - D. Twinning
9. Most effective wave length of light in phototherapy is:
 - A. 450–460
 - B. 550–650
 - C. 300–350
 - D. 200–250
10. Spot the wrong observation:
 - A. Physiological jaundice is seen in around 60–70% neonates
 - B. Neonatal jaundice appearing in first 24 hours is always pathological
 - C. Phototherapy may cause dark grey brown pigmentation (bronze baby syndrome)
 - D. Rise in serum bilirubin is greater than 0.5 mg/dL every hour is in keeping with physiological jaundice
11. Blood requirement for double volume exchange transfusion:
 - A. 160 mL/kg
 - B. 240 mL/kg
 - C. 100 mL/kg
 - D. 200 mL/kg
12. Conjugated hyperbilirubinemia denotes conjugated serum bilirubin:
 - A. Greater than 15–20% of the total
 - B. 25–30%
 - C. 10–15%
 - D. 3–10%
13. Spot the wrong entry:
 - A. Erb palsy—C5, C6
 - B. Klumpke's paralysis—C7, C8, T1
 - C. Cephalhematoma—molding
 - D. BCG vaccine—intradermal
14. A term neonate loses upto 10% weight in first week of life. When does he regain the loss?
 - A. By 10 days of age
 - B. By 15 days of age
 - C. By 21 days of age
15. Spot the wrong entry regarding duration of antimicrobial therapy in neonatal infections:
 - A. Culture-positive sepsis 2 weeks
 - B. Meningitis 3 weeks
 - C. Osteomyelitis 4 weeks
 - D. Empirically started therapy not supported by subsequent observations/culture 5 days
16. Spot the organ/ body part that is virtually spared in asymmetrical IUGR:
 - A. Brain
 - B. Lungs
 - C. Subcutaneous fat
 - D. Muscles
17. Spot the danger sign for the neonate:
 - A. Not passing urine by 24 hours of birth
 - B. Not passing stool by 12 hours of birth
 - C. Cold clammy skin
 - D. Erythema toxicum

18. Spot the wrong entry about Moro reflex:
 - A. Incomplete at 28 weeks
 - B. Complete by 32 weeks
 - C. Exaggerated in kernicterus
 - D. Disappears by 3 months.
19. A newborn with drooling of saliva with respiratory distress on the very first day of life is most likely suffering from:
 - A. Tracheoesophageal fistula
 - B. Congenital diaphragmatic hernia
 - C. Immature lung syndrome
 - D. Achalasia cardia.
20. Most likely cause of vomiting on very first day of life is:
 - A. Tracheoesophageal fistula
 - B. Congenital pyloric stenosis
 - C. Meconium aspiration gastritis
 - D. Aerophagia

Answers

- | | | | | | |
|-------|-------|-------|-------|-------|-------|
| 1. C | 2. B | 3. D | 4. C | 5. B | 6. C |
| 7. A | 8. B | 9. A | 10. D | 11. A | 12. A |
| 13. C | 14. A | 15. C | 16. A | 17. C | 18. C |
| 19. A | 20. C | | | | |

Clinical Problem-solving**Review 1**

A breastfed term neonate's physiological jaundice, rather than regressing, shows uphill trend, rising to 18 mg/dL (direct 2.1 mg/dL, indirect 15.9 mg/dL) by 16 days. Else, he appears well without any feeding difficulty or other problem.

1. What could be the most likely cause of exaggerated hyperbilirubinemia in this baby?
2. Which other conditions fall in the differential diagnosis?
3. What is the fundamental cause in the likely diagnosis in the baby?
4. How will you manage it?
5. What about over anxious parents who won't accept your logical advice?

Review 2

A preterm neonate of 30 weeks gestation develops respiratory distress with tachypnea, grunting, chest retractions and cyanosis some 4–5 hours after birth. CXR shows "white-out" lungs. A diagnosis of severe respiratory distress syndrome is made. However, response to CPAP and mechanical ventilation is poor.

1. What should be the therapeutic approach in this situation?
2. What's the prognosis?
3. Could the problem be prevented by an antenatal action?
4. Which such antenatal action will you prefer?
5. Any contraindications to such a therapy?

Review 3

A premature neonate, aged 6 days, is on treatment for sepsis. Just when he looks like improving, he develops progressively increasing abdominal distention, vomiting, blood in stools, and diminished bowel sounds.

1. What is the most likely cause of fresh symptoms and signs?
2. How to confirm the diagnosis?
3. What can be the complications in case of delayed or inappropriate treatment?
4. Are there any sequelae of this disease?

Answers**Review 1**

1. Breast milk jaundice.
2. A large cephalhematoma, congenital hypothyroidism, intrauterine infections (TORCH), polycythemia, hypoxia, congenital heart disease, delayed passage of meconium, etc.

contd...

3. The 3-alpha, 20 beta pregnandiol and free fatty acids in mother's milk. These substances inhibit conjugation of bilirubin.
4. Being a self-limiting condition, it resolves on its own without any intervention.
5. In such a situation, a temporary withdrawal of breastfeeding just for 2–3 days resolves the problem.

Review 2

1. This neonate with severe RDS, certainly is in need of exogenous intratracheal surfactant therapy. Simultaneously, ventilator should be continued.
2. Timely administration of surfactant along with CPAP and ventilator support can save 90% of the babies. Else, a majority of the babies with severe RDS are likely to die.
3. Antenatal steroids, administered when labor is less than 35 weeks, can reduce the incidence and severity of RDS.
4. Preferred steroid is betamethasone, 12 mg IM, 24 hourly, for 2 doses.
5. Toxemia of pregnancy and chorioamnionitis are contraindications to antenatal steroid therapy.

Review 3

1. Neonatal necrotizing enterocolitis.
2. X-ray showing dilated intestinal loops with pneumatosis intestinalis is diagnostic for NEC.
3. Complications include shock, apnea, acidosis, DIC, acute kidney injury, peritonitis, pneumoperitoneum and perforation, etc.
4. Intestinal strictures, short bowel syndrome with malabsorption.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS/INTERNET

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1. Gupte S, Gupte SB, Gupte M (eds). *Recent Advances in Pediatrics (Special Vol. 25: Perspectives in Neonatology)*. New Delhi: Jaypee 2014.
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SECTION 4

Pediatric Infections

Section Outline

18. Viral Infections
19. Bacterial Infections
20. Fungal Infections
21. Protozoal Infections and Infestations
22. Helminthic Infections and Infestations
23. Intrauterine Infections
24. Nosocomial, Anaerobic and Opportunistic Infections
25. Fever Spectrum

SMALLPOX**(Variola)**

Smallpox, a highly contagious disease of man, known since its earliest description by Sushruta, the Father of Plastic Surgery, in 600 BC, became a part of history in early 1980s. Thanks to the World Health Organization (WHO) massive eradication program.

A large deoxyribonucleic acid (DNA) virus, belonging to the poxviruses, was the etiologic agent (Figs 18.1).

Though it was in 1980 that smallpox was declared as **eradicated worldwide**, the smallpox vaccine seed virus (vaccinia virus strain Lister Elstree) is maintained in the WHO collaborative center on smallpox vaccine at the National Institute of Public Health and Environmental Protection in Bilthoven, Netherlands. The aim is to be in a position to produce new stock of vaccine as and when needed.

MONKEYPOX: A NEW CHALLENGE

Despite the worldwide eradication of smallpox, we continue to have monkeypox as a sporadic disease in parts of Africa. The virus is related to the virus that caused smallpox and may cause clinical presentations in humans similar to those seen in smallpox cases in the past. The outbreak in Zaire (Republic of Congo) happened to be the largest cluster of monkeypox cases ever recorded as per 1997 report of the WHO.



Fig. 18.1: Classical smallpox. Note the predominantly peripheral distribution of the rash with hard shotty feel and at the same stage of development.

POLIOMYELITIS

Thanks to the herculean endeavors under WHO, poliomyelitis*, a leading cause of disability, is on the verge of eradication just like smallpox. Mercifully, India has been polio-free since January 2011.

Etiological Considerations

Polio is caused by a ribonucleic acid (RNA) enterovirus. Three antigenically distinct strains are known: type 1—Burnside, type 2—Lansing, type 3—Leon with type 1 accounting for 85% of cases of paralytic illnesses. Infection with one type does not protect from the other types; however, immunity to each of the three strains is lifelong.

Transmission and Spread

Polio spreads by the fecal-oral route and by aerosol droplets. Multiplication occurs in gastrointestinal tract (GIT), related lymph nodes and reticuloendothelial system. Then, there is viremia of short duration. If the antibody formation fails to neutralize virus particles, there results proliferation of the virus and invasion of the nerve structure.

Anterior horn cells, bulbar nuclei and cerebellar cortex are primarily affected. Clinical picture depends on the number and location of involved neurons. A vast majority of the paralytic cases occur below the age of 3 years with the peak incidence at 2 years.

Clinical Features

- **Incubation period:** It is 7–14 days (range 5–35 days).
- **Clinical types:** Asymptomatic (silent), abortive non-paralytic and paralytic. Paralytic polio may be spinal, bulbar, bulbospinal or encephalitic, depending on the location of the lesions.
- **Recovery/convalescent stage:** It is characterized by disappearance of the acute symptoms and muscle tenderness and recovery of the paralyzed muscles. Rapid recovery may occur in the first 6 months.
- **Residual-paralysis stage:** The period beyond 2 years after the onset of the disease is characterized by development of deformities due to imbalance of muscle power and poor posture, disuse atrophy of muscles, shortening of the leg due to interference with growth, and, in neglected cases, gross fixed deformities of the hip, knee and foot with severe wasting of muscles (Fig. 18.2). Children with extensive paralysis and gross deformities have to crawl on all four limbs to move from place to place.

* President Roosevelt of United States had suffered from polio in 1921.



Fig. 18.2: Post-polio residual deformities (PPRD). Note the wasted right lower limb with genu recurvatum.

Table 18.1: Differential diagnosis of poliomyelitis	
Pseudoparalysis	Neurologic conditions
<ul style="list-style-type: none">• Acute osteomyelitis• Septic arthritis• Periostitis• Sprain• Syphilis• Scurvy• Trichinosis• Rheumatic fever• Severe hypokalemia	<ul style="list-style-type: none">• GBS• Transverse myelitis• Traumatic neuritis• Post-diphtheretic paralysis• CNS infection (meningitis, encephalitis)• Botulism

Abbreviations: CNS, central nervous system; GBS, Guillain-Barré syndrome.

Diagnosis

In a large majority of the cases, diagnosis of paralytic polio is clear from the clinical profile. An acute onset of asymmetrical flaccid paralysis must arouse a suspicion of poliomyelitis.

Differential Diagnosis (Table 18.1)

- Pseudoparalysis (scurvy, acute osteomyelitis, trauma, etc.)
- Guillain-Barré syndrome (GBS), transverse myelitis and traumatic neuritis
- Meningitis, encephalitis, meningismus
- Post-diphtheritic paralysis.

Treatment

Residual paralysis needs treatment. The final aim should be for patients to return home and be accepted and integrated into their communities. Since overuse weakness is frequently present in these patients, the role of slowly progressive, nonfatiguing exercise in their rehabilitation is crucial. New muscle weakness of a mild to moderate degree responds well to a nonfatiguing exercise program and pacing of activity, with rest periods to avoid muscle overuse. Generalized fatigue may be treated with energy conservation, weight loss programs and lower extremity orthoses.

An **orthosis** is a device that externally supports an existing body part, with the objective of supporting, correcting, or compensating for skeletal deformity or weakness. There are currently many various types of orthoses, and the range of devices available to the prescriber continues to increase with the advent of new materials such as carbon fiber, as well as advances in manufacturing techniques. Orthoses are available for all parts of the body and aid in conservative and definitive treatment for many deformities. The thermoplastic leaf spring ankle foot orthosis, or drop foot splint, is one good example of an orthosis commonly used. It assists dorsiflexion and uses 3 point pressure to stabilize the ankle joint.

Prophylaxis

Immunization against poliomyelitis has got to be continued in a modified way with gradual spill over from oral polio vaccine (OPV) to inactivated polio vaccine. For details, See Chapter 10 (Immunization).

POST-POLIO SYNDROME

Definition

Post-polio syndrome is characterized by new neurologic, musculoskeletal and general manifestations that develop in 25–60% of polio patients, 30–40 years after the occurrence of the acute illness.

Musculoskeletal manifestations include muscle pain, joint pain, spinal changes such as spondylosis and scoliosis, and secondary root and peripheral nerve compression. General manifestations include generalized fatigue and cold intolerance. The slowly progressive muscle weakness occurs in those muscle groups already involved, such as the quadriceps and calf muscles.

Etiopathogenesis

The specific cause of post-polio syndrome is unknown; the etiology has been attributed to pathophysiological and functional causes.

- **Pathophysiological causes** include chronic poliovirus infection, death of the remaining motor neurons with ageing, premature ageing, and damage to the remaining motor neurons caused by increased demands or secondary insults, and immune-mediated syndromes.
- **Functional etiologies** for post-polio syndrome include greater energy expenditure as a result of weight gain and muscle weakness caused by overuse or disuse.

Post-polio syndrome has been recognized for over 100 years, but it is more common at the present time because of the large epidemics of poliomyelitis that occurred in the 1940s and 1950s.

Diagnostic Criteria

- A prior episode of paralytic poliomyelitis with residual motor neuron loss (which can be confirmed through a typical patient history, a neurologic examination, and, if needed, an electrodiagnostic examination).
- A period of neurologic recovery followed by an interval (usually 15 years or more) of neurologic and functional stability.

- A gradual or abrupt onset of new weakness or abnormal muscle fatigue (decreased endurance), muscle atrophy, or generalized fatigue.
- Exclusion of medical, orthopedic and neurologic conditions that may be causing the symptoms mentioned above.

Management

Many patients require revision of orthotic devices such as braces, canes and crutches or may use new, lighter orthotic devices to treat new symptoms. Common issues include genu recurvatum, knee pain, back pain, degenerative arthritis or arthralgia. Surgery for scoliosis or fractures may also be necessary to treat new conditions.

GUILLAIN-BARRÉ SYNDROME

Guillain-Barré syndrome (GBS) is characterized by symmetrical ascending paralysis with some sensory loss in majority of the instances. Involvement of respiratory muscles may prove fatal. A typical cytoalbuminous dissociation in the cerebrospinal fluid (CSF) is its important feature. For more details, refer *See* Chapter 28 (Pediatric Neurology).

ACUTE FLACCID PARALYSIS SURVEILLANCE

Definition

The term, *acute flaccid paralysis (AFP)*, means that the paralysis is acute in onset, less than 4 weeks and the involved limbs are flaccid (floppy or limp).

Etiology

Poliomyelitis is the most important cause of AFP in children. The non-polio causes of AFP include GBS, transverse myelitis (TM) and traumatic neuritis (TN).

AFP Surveillance

Aimed at detection and eradication of poliomyelitis, AFP surveillance aims at detecting cases of AFP (under 15 years age) and reporting them immediately to the District Immunization Officer of the area. This should not be interpreted as meaning that only cases of polio are to be reported. All types of AFP (including GBS, TM, TN, hypokalemia, scurvy, encephalitis, etc) cases require to be reported so that there is no chance of missing any case of polio. Expected non-polio AFP rate is more than 1 in 100,000 children under 15 years of age in a year (background rate formed by GBS, TM and TN).

Special Features

- **Reverse cold chain:** Stool samples (two, at least 24 hours apart, within 14 days of onset of paralysis) from each AFP case are obtained and transported to the laboratory within 72 hours of collection (at 4–8°C or frozen at minus 20°C) for virological identification and, if found to be poliovirus, for finding whether it is a natural wild virus or vaccine-related virus.
- **Outbreak response efforts:** These should be initiated promptly without waiting for the stool culture reports

which may take 4–8 weeks. All cases labeled as **dis-** **333**
carded, not polio require thorough justification and should be reported with final diagnosis.

Indicators of Quality

- Non-polio AFP rate more than 1 in 100,000 children under 15 years (annual).
- At least 80% of AFP cases whose two adequate stool samples have been examined.

Role

- To identify high-risk areas or groups where polio virus transmission is occurring or is likely to occur.
- To monitor progress so as to determine whether strategies are implemented effectively.
- To certify a country polio-free when no reports of new cases of polio are received for 3 consecutive years; and that the country can detect a case of paralytic polio should it occur through importation. Also *See* Chapter 10 (Immunization).

Mopping up denotes the final strategy when door to door polio immunization is provided in high-risk districts, i.e. where polio cases are detected in the preceding 3 years.

VARICELLA (CHICKENPOX)

It is also termed as **chickenpox**, is a highly communicable though generally mild exanthematous viral infection in healthy children. In adolescents, adults, neonates and immunocompromised subjects, it tends to be rather serious with complications like varicella bronchopneumonia and high morbidity and mortality.

Unlike smallpox, chickenpox does not always confer permanent immunity and second attack infrequently occurs. There is no age bar, though a large majority of the cases are young children (5–10 years).

Etiopathogenesis

The causative agent is a DNA virus, varicella zoster virus (VZV), which may remain latent and cause herpes zoster in later life.

The mode of transmission resembles that of smallpox. The portal of entry of the virus is respiratory tract. The spread is by direct or indirect contact with respiratory secretions or skin lesions of patients; air-borne infection is rather uncommon.

Secondary attack rate (involvement of the nonimmune inmates of the house) is as high as 80–90%. Period of infectivity extends from 24–48 hours before appearance of rash until formation of scabs (crusts) which are noninfectious.

Epidemiology

Chickenpox is worldwide in distribution, occurring in both temperate and tropical regions. It shows some seasonal variation, the peak incidence being during winter and summer (January–May).

The peak age of incidence is 5–10 years, though the disease may occur at any age including neonatal period,

334 adolescence and adulthood, when it frequently takes a serious turn. Dominant pathologic changes are limited to skin and to some extent to the respiratory tract.

The patient is infective to others a day or two (24–48 hours) before and around 5–7 days after appearance of rash (until formation of crusts/scabs). Exposure to herpes zoster may cause initiation of chickenpox epidemic.

Clinical Features

Incubation period is around 15 days, the range being 11–21 days. The **prodromal phase** of slight malaise, low-grade fever, headache, backache, anorexia and shivering is short (just 24 hours) and may not be noticed.

Thus, the onset may be sudden with appearance of a rash, the first sign in majority of the cases. The eruption passes through all the stages encountered in smallpox, i.e. macule, papule, vesicle, pustule and crust (Fig. 18.3). The progression of the rash is, however, much rapid. The complete evolution takes about 4–7 days followed by scab formation. The scabs (crusts) fall off within 2 weeks of first appearance of rash. These are not infective since virus is present in vesicles and not in crusts.

Skin lesions of chickenpox appear in 2–4 crops so that all stages and sizes may be seen at the same time. Furthermore, these are superficial, pleomorphic and centripetal in distribution and are seen over the scalp and mucus surfaces (including conjunctiva) first and then over the body. The trunk is profusely covered whereas extremities and face are only scantily involved. Axilla is affected, but the palm and sole are usually spared.

On an average, around 10–500 (with a median of 300) pleomorphic lesions are encountered in an individual subject. Chickenpox lesion on healing leave behind macules (hypo or hyperpigmented) for a week or more but, eventually, without scar unless secondary infection occurs. Occasionally in children under 2 years of age, chickenpox lesions may be in the form of bullae rather than vesicles. This variant of the disease is termed as **varicella bullosa**.

The constitutional symptoms include some fever when most vesicles have reached the pustular stage. Itching is mild at first, but may become severe in the pustular stage.



Fig. 18.3: Varicella. Note the pleomorphic centripetal lesions in a 10-year-old patient.

Box 18.1

Congenital varicella syndrome (varicella embryopathy)

• Maximum risk	8–20 weeks of gestation.
• Cause	Virus-induced injury to central nervous system (CNS) with predilection for tissues that are in a rapid developmental stage like limb buds.
Stigmata	
• Skin	Cicatrix presenting as a zig-zag scarring in a dermatomal distribution; hypopigmentation.
• Brain	Aplasia, microcephaly, hydrocephaly and calcification.
• Spinal cord	Shortened or malformed limbs, motor/sensory deficit, absent deep tendon reflexes, anisocoria, Horner syndrome, anal and urinary sphincter dysfunction.
• Eye	Microphthalmia, cataracts, optic atrophy and choreoretinitis.

Hemorrhagic, neonatal and even congenital chickenpox may infrequently be seen. In case the mother develops chickenpox between 5 days before and 5 days after delivery, 15–20% neonates develop this infection. Mortality in them is as high as 30%. Maternal infection may damage the fetus, causing **embryopathy** with limb atrophy, scarring of skin, malformations in relation to extremities and ophthalmic (cataracts) and meningeal and brain lesions (calcifications, aplasia), the so-called **congenital varicella syndrome** (Box 18.1).

Diagnosis

It is more or less clinical. The disease had got to be differentiated from smallpox in by gone era. Early in disease, the papules of chickenpox may need to be differentiated from pyoderma, insect bite, papular urticaria, drug reaction, herpes simplex, hand-foot-mouth disease and rarely, molluscum contagiosum.

Laboratory diagnosis is difficult. White blood cells (WBC) count is usually normal or little low, except in event of a superadded bacterial infection when it is high with polymorphonuclear response. In the fluid from skin lesions, multinucleated giant cells containing intranuclear inclusions and immunoglobulin M (IgM) antibodies may be demonstrated.

Remaining confirmatory tests include immunofluorescent staining of scrapings from vesicles with monoclonal antibodies, indirect fluorescent antibody, latex agglutination and enzyme linked immunosorbent assay (ELISA).

Complications

In a majority of the cases, chickenpox runs a benign course. The potential complications are listed in Box 18.2. The so-called **progressive varicella syndrome** is a very serious condition characterized by nonstop eruption of varicella lesions which have a tendency to become hemorrhagic secondary to a coagulopathy and multiorgan involvement in the form of hepatitis, pneumonia and encephalitis. It usually occurs in immunocompromised states, neonates, adolescents and adults.

Box 18.2 Complications of chickenpox**Cutaneous**

- Superadded skin infection with *Streptococci* or *Staphylococci*, i.e. cellulitis, abscess, etc
- Purpura fulminans (from DIC)
- ITP.

Systemic

- Bronchopneumonia usually due to superadded bacterial infection; rarely varicella pneumonia.
- Neurologic—encephalitis (including Reye's syndrome), cerebellar ataxia, transverse myelitis, polyradiculitis, GBS, facial nerve palsy, optic neuritis with transient loss of vision, a hypothalamic syndrome with recurrent pyrexia and obesity, etc
 - Septicemia
- Suppurative arthritis/osteomyelitis
- Myocarditis
- Bleeding diathesis due to thrombocytopenia or DIC
- Glomerulonephritis
- Hepatitis
- Appendicitis
- Myositis
 - Reye's syndrome (if aspirin given)
 - Herpes zoster (late complication).

Abbreviations: DIC, disseminated intravascular coagulation; ITP, idiopathic thrombocytopenic purpura; GBS, Guillain-Barré syndrome.

Subsequently, herpes zoster in its mild form with a slight rash with dermatomal distribution and only mild pain may occur in children who had varicella, especially in those with immunocompromised status.

Treatment

No specific treatment is available. General and supportive measures include:

- Antipyretics for fever are given. Aspirin, however, needs to be avoided since it may enhance the risk of developing Reye syndrome in subjects with varicella.
- Itching may be relieved by systemic antihistaminics and/or local application of calamine lotion, potassium permanganate, etc. and sponge baths with antiseptic detergents.
- Nails must be cut short.
- Mouth and perineal regions may be treated by rinses, gargles and saline soaks. Secondary infections require appropriate antibiotics. In varicella pneumonia, antibiotics are not of much value.
- Steroids are, as a rule, contraindicated.
- General measures for encephalitis are outlined in Chapter 28 (Pediatric Neurology).
- Children suffering from chickenpox must be restrained from attending the school for 6 days after the appearance of the rash, i.e. until all lesions are converted into crusts/scabs.
- Acyclovir (Zovirax) claims to accelerate rate of clinical and skin lesion improvement, to reduce number of skin lesions, and to cause speedy defervescence. The therapy is quite expensive. Until more convincing evidence becomes available for its utility in routine cases of chickenpox, its administration should be

restricted to immunocompromised subjects who develop chickenpox or varicella pneumonia. The dose is 20 mg/kg/dose 4 times daily for 5 days.

- Parenteral intravenous (IV) acyclovir is reserved for varicella in immunocompromised subjects, neonates and pregnant women and in complicated varicella (say with pneumonia).

Prophylaxis

A live attenuated varicella vaccine which gives an efficacy of 80% in safeguarding against the disease and also following exposure (provided that it is administered within 3 days of exposure to a case of chickenpox) or significantly reducing the intensity of the disease, is given in two doses subcutaneously. The vaccine is quite safe and well tolerated but expensive. Mild to moderate rash may appear in some cases.

Varicella zoster immunoglobulin (VZIG) is indicated for inducing passive immunity (postexposure prophylaxis) in the following situations:

- Children at high-risk of severe varicella, e.g. immunocompromised states like immunodeficiency diseases, leukemia or malignancies, and those on immunosuppressive drugs.
- Neonates whose mothers develop varicella within 2 days before and 5 days after delivery.
- Probably susceptible pregnant women exposed to varicella, especially if antibody testing turns out to be negative. The recommended dose of VZIG is 125 units/10 kg and that of ZIG 5 mL intramuscularly (IM).

Schools must insist on isolation of children with chickenpox at least until 6 days of appearance of the rash to safeguard against an epidemic.

Prognosis

Chickenpox carries, as a rule, favorable prognosis. Nevertheless, complications such as varicella pneumonia and encephalitis, especially in immunocompromised hosts, may prove fatal.

MEASLES (Rubeola)

It is the most common and the most infectious of the viral infections of childhood, causing considerable morbidity and mortality (around 75,000 deaths annually in India alone). It is characterized by catarrhal symptoms followed by a typical rash, the so-called *measly rash*.

It is a frequent cause of ill health, morbidity and mortality, especially in the undernourished infants and children below the age of 3 years. In healthy children, it generally runs a more or less benign course.

It is unusual before the age of 3–4 months and mild in the next 6 months. This is because of the protection provided by the maternal antibodies. The peak incidence in the developing world is in the age group 1–5 years. One attack confers nearly lifelong immunity.

336 Etiopathogenesis

The causative agent is the specific measles virus, an RNA virus (paramyxovirus group*). Transmission is by indirect or direct contact and droplet infection, portal of entry being respiratory tract. It is in the epithelium of the respiratory tract that the virus multiplies. From the airway epithelium, occurs the primary viremia that leads to involvement of the reticuloendothelial system (RES). Later, systemic manifestations result from secondary viremia. The period of infectivity is 4 days prior to and 5 days after the appearance of the rash. Pathological changes are essentially limited to superficial blood vessels of skin and mucous membrane, forming the so-called *inclusion bodies*.

Epidemiology

Measles is a worldwide disease. Both epidemic and endemic forms occur. Highest incidence is in winter and spring. Poorer the community, higher the occurrence of the infection at lower age. The infection is highly contagious with secondary attack rates as high as over 90% in susceptible (unimmunized) household contacts.

The disease is the focus of strange beliefs. As for instance, it is generally regarded as *Curse of the Goddess*. Either no medicines or the ones which are supposed to cause greater eruption are preferred by the folklore. Harmful practices such as fomentation with hot bricks, instilling cow milk drops in nostrils and eyes, and giving a purge in order to bring the rash out fully are common. Also, during the illness, the *child should receive only negligible food or fluids*. It is generally held that measles is not a good reason to consult a doctor. Instead, the parents prefer to visit the temple. All this adds up to the problems of the child with measles.

Clinical Features

The average incubation period is 11 days, the variation being between 10 days and 12 days provided that onset is ascribed to the first prodromal symptoms. Three stages are known—prodromal, eruptive and convalescent.

1. **Prodromal (Catarrhal) phase** of 3–5 days is characterized by upper respiratory catarrh (rhinorrhea, dry cough), fever, malaise, conjunctival congestion and photophobia. Posterior cervical lymphadenopathy may accompany these early manifestations. Another important feature of this phase is the appearance of the Koplik's spots. There are fine, tiny grain-like papules, white or gray, on faint erythematous base. Their first appearance, usually on second or third day, is over the buccal mucosa, opposite the first or second lower molar, and then at other sites in the mouth. Koplik's spots are pathognomonic of measles and usually disappear by about fifth day, a day after the rash which appears around fourth day. In practice, these are observed in only a small proportion of cases.
2. **Eruptive phase** is characterized by a rash (Figs 18.4A to C) which appears 3–5 days after the onset of the

*Mumps and parainfluenza also belong to this group.



Fig. 18.4A: Measles: Note the classical pink, blotchy, irregular macular rash first involving the face and retroauricular area.



Fig. 18.4B: Measles: Note the rash spreading over body parts.



Fig. 18.4C: Measles: Note the rash spreading over body parts.

disease. With the appearance of rash, fever tends to regress, but takes another 3 days to disappear. The rash is seen far better in day light than in artificial light. Its special features are:



Fig. 18.5: Severe measles. Note the widespread confluence of maculopapular rash. Frequency of complications is relatively higher in such cases with guarded prognosis.

- Pink, blotchy irregular macular erythema. It fades on pressure and quickly darkens and blends into large red patches of varying size and shape.
 - Face and areas behind the ears (retroauricular area) are the sites of its first appearance. Then it spreads to neck, trunk and limbs during the following 3–4 days. It is frequently accompanied by cervical lymphadenopathy days.
 - It lasts for 4–7 days. Mild itching may accompany it. The rash starts fading from third to fourth day, disappearing in the order of appearance.
 - Eventually, there results a fine shedding of the superficial skin of face followed by that of trunk and limbs, leaving behind a light-brown pigmentation. It takes 10–14 days for the pigmentation to fade.
 - Severe measles with highly profuse and widespread maculopapular rash (Fig. 18.5) carries more risk of complications. Infrequently, measles may be complicated by bleeding from different sites and a purpuric rash (*hemorrhagic measles*).
3. **Convalescent phase** is marked by disappearance of fever, other constitutional symptoms and the rash. Clinical picture in a partially immune child may be of a mild illness of short duration (*modified measles*).

Diagnosis

It is primarily clinical, needing no investigations.

- The leukocyte count is low, but slowly rises to normal as the rash fades. In case of superadded bacterial infections, a sharp leucocytosis often occurs.
- Measles-specific IgM antibody appears 3 days after the rash and persists for 30–60 days following the rash.
- ELISA and hemagglutination inhibition are the most sensitive for detecting measles antibodies which, if increased 4 times, are diagnostic of measles.

* Interestingly, the rash often becomes manifest following administration of ampicillin.

- Today, it has become possible to isolate the virus from the nasopharynx or blood, especially during the acute stage.
- Even 10–20 days after the onset, complement-fixation antibodies in meaningful titer may be detected.

Differential Diagnosis

- At times, another supposedly viral infection of infant and toddlers, *roseola infantum* (roseola subitum, fifth disease), may be confused with measles. The pink macular rash of this infection usually appears on trunk, neck and proximal areas of the extremities only. It lasts for just 24 hours as against measles in which the rash lasts for 4–7 days. Moreover with its appearance fever disappears. In measles, there is an overlap of fever and rash for a day or so. During this short span, fever may show a hike.
- In *rubella*, the rash is discrete and mild. There is significant posterior occipital lymphadenitis. Prodromal phase is slight and short.
- **Infectious mononucleosis** (glandular fever) is characterized by rash*, fever, generalized lymphadenopathy and hepatosplenomegaly. It is caused by Epstein-Barr virus (EBV) and is benign.
- In *drug rash*, a history of the rash following intake of a drug may be of help.
- In *meningococcemia*, rash has a tendency to become petechial and other signs of the disease, such as meningitis, toxemic state of the patient, etc. are usually present.
- In *typhus*, the rash is centripetal. The patient is very toxic.
- *Miliaria rubra* (prickly heat, sudamina and heat rash) causes pinhead sized erythematous papules over the areas where sweat glands are in abundance. It is usually seen in summer.
- **Kawasaki disease**, over and above the rash, is accompanied by other manifestations such as cervical lymphadenopathy, glossitis and edema of hands.

Complications

The potential dangers of measles lie in its complications (Box 18.3) rather than in the disease per se.

Treatment

No specific treatment is available. General measures consist of:

- Isolation
 - Medications—cough sedatives, vasoconstrictor nasal drops, antipyretics and antihistaminics for itching
 - Attention to eye and mucus membrane of mouth
 - Maintenance of proper fluid and dietary intake
 - Vitamin A administration to reduce the morbidity from measles
 - In case bacterial infection is superimposed, suitable antibiotic(s) should be given.
- Antiviral agents are not of proven value. γ -globulins, hyperimmune γ -globulins and steroids are of doubtful value.

Immediate complications

- Otitis media tops the list of respiratory complications.
- Tracheobronchitis, laryngotracheobronchitis, bronchiolitis, bronchopneumonia subcutaneous emphysema* etc. Rarely, measles virus may spread to the lung parenchyma, causing the so-called **giant-cell pneumonia** which may prove fatal. Measles pneumonia in AIDS may occur without any rash. It often proves fatal.
- Stomatitis, enteritis and even cancrum oris (noma), especially in malnourished children.
- Activation of existing tuberculosis with transient loss of hypersensitivity to tuberculin.
- Keratitis and corneal ulceration secondary to vitamin A deficiency that commonly follows measles.
- Bleeding diathesis, the so-called **hemorrhagic measles**. It has a stormy onset with high fever, convulsions, delirium, coma and bleeding. Also termed **black measles**, it has a fatal outcome.
- Appendicitis.
- Malnutrition.
- Encephalitis is rare (just 0.1 %) but the most dreadful of all. The survivors are invariably left with residual sequelae, including mental retardation.
- Remaining CNS complications such as GBS, cerebral thrombophlebitis, hemiplegia, and retrobulbar neuritis are still rarer.
- Acute glomerulonephritis.
- Steven-Johnson syndrome.
- Decreased cell-mediated immunity and anergy (during few weeks after attack).
- Transient ECG changes and myocarditis (uncommon).

Late complication

- Very rarely, SSPE, a universally fatal disease, may result as a long-term sequelae on an average of 6 years (range 3-6 years) after the attack of measles. It is characterized by myoclonic jerks and mental deterioration. It behaves like a degenerative disorder.

Abbreviations: AIDS, acquired immunodeficiency syndrome; GBS, Guillain-Barré syndrome; CNS, central nervous system; ECG, electrocardiogram; SSPE, subacute sclerosing panencephalitis.

* Other cause of subcutaneous emphysema includes trauma, asthma, pertussis, foreign body and violent cough, etc.

Prophylaxis

- Isolation of the affected child is warranted.
- Active immunization is provided by measles vaccine at 9 months and then at 15-18 months in the form of measles, mumps and rubella (MMR) vaccine as detailed in Chapter 10 (Immunization)
- Passive protection can be achieved with γ -globulins in the following situations:
 - 0.2 mL/kg to prevent occurrence of measles in debilitated susceptible contacts unable to withstand the illness
 - 0.04 mL/kg to healthy susceptible contacts in whom it is desirable to have mild attenuated measles.

RUBELLA**(German Measles,* Three-day Measles)**

Rubella is a relatively less contagious viral infection, characterized by mild prodromal symptoms, a typical eruption and enlargement of cervical lymph nodes. It is primarily a disease of older children and adults. Second attack is rare.

* Thus named since it was earlier thought to be a variant of measles by the German physicians.

* No teratogenic effects on fetus are seen if rubella occurs in mother after 16 weeks of gestation.

Etiopathogenesis

The causative agent is a myxovirus. Transmission is by droplet infection and direct contact. The virus enters the host through the upper respiratory route. The period of infectivity is 5 days prior to and 4 days after appearance of rash.

Clinical Features

Incubation period is around 16 days. The range is 14-21 days. **Prodromal phase** lasts for a few days. Slight malaise and, occasionally, tender posterior cervical lymphadenopathy without any catarrh may be there. The phase may be entirely absent or remain unnoticed. **Rash** may be the first visible sign. This is especially so in case of small children. To start with, it is a macule which spreads from face to trunk and extremities. Macules later blend. The eruption disappears by the third day. There may be slight fever for 2 days. In certain instances, rash may not appear at all. In this situation, febrile lymphadenopathy may be there for a week or more.

Congenital Rubella Syndrome

Over the years, there has been a growing recognition of the fact that infants born to mothers who had suffered from rubella in the first trimester (more so first month)** of pregnancy, invariably suffer from multiple congenital defects. This condition has been called the **congenital rubella syndrome**. In 1960s, a more detailed picture of this syndrome emerged, earning it the name extended (or expanded) congenital rubella syndrome. Its important manifestations are:

■ **Classical triad**

- Deafness
- Congenital heart disease (patent ductus arteriosus)
- Rubella cataract (Fig. 18.6).

■ **Others**

- Growth retardation, mental retardation and microcephaly, hepatosplenology, hepatitis, thrombocytopenia and purpura, otitis media, pancreatitis, pneumonitis, cerebral diplegia, cleft palate and lip, syndactyly,



Fig. 18.6: Rubella cataract.

spina bifida and talipes equinovarus, dental malformations, microphthalmia, buphthalmos and retinal lesions (salt and pepper retinitis).

Progressive rubella panencephalitis is exceedingly rare chronic encephalitis as a result of persistent rubella virus infection of the central nervous system (CNS). The illness behaves like subacute sclerosing panencephalitis (SSPE). Rubella virus has been isolated from brain cell culture and from separated blood lymphocytes of these patients.

Diagnosis

Clinical suspicion is of vital importance. Diagnostic tools include:

- **Serological tests:** Demonstration of positive rubella IgM in neonate's blood (including cord blood) is considered sufficient for diagnosis. Neutralization, complement fixation, hemagglutination inhibition, fluorescent antibody studies, ELISA, etc. are also available.
- **Virus isolation:** In a newborn with congenital rubella syndrome, virus can be recovered from nasopharyngeal washings, CSF, blood, stools or urine. This virus may persist until the baby is of 12–18 months of age.

Treatment

Unfortunately, there is nothing specific (not much otherwise too) at physician's command as far as treatment is concerned. Treatment with agents such as interferon or isoprinosine has not yielded encouraging results. If complications like encephalitis, polyarthritis, neuronitis, etc. are present, these should be tackled accordingly.

Prophylaxis

The only reliable means of preventing rubella is the administration of the vaccine (rubella vaccine as such or MMR) to all children. In case of catch-up situation, all adolescent girls should be given the vaccine to reduce the burden of rubella during pregnancy and its consequences in the form of congenital rubella syndrome. γ -globulin, though employed in the past, is of doubtful value.

MUMPS

(Epidemic Parotitis)

This not-so-contagious viral disease is characterized by painful swelling of the salivary glands (especially the parotids) and, frequently, by CNS involvement. An overwhelming majority of sufferers (85%) belong to pediatric age group. A single attack leads to lifelong immunity.

Etiology

An RNA virus (genus: *Paramyxovirus*, family: Paramyxoviridae) with a solitary serotype is the causative agent. In around 10% cases, the virus has a tendency to attack the neural tissue, causing aseptic CNS infection (encephalitis and meningitis)

Epidemiology

Mumps has a worldwide spread, the incidence being much higher in cities than in rural areas. Peak incidence occurs

in late winter and spring. About 30–40% infections are subclinical.

Infection occurs by direct contact, indirect contact (contaminated fomites) or airborne droplets. The portal of entry is the upper airway. In the epithelium of the airway, mumps virus proliferates, and then makes its entry into the blood circulation and finally settling in the glandular and neural tissues. Secondary infection rate is very high (around 80%).

Clinical Features

Most cases are in 5–15 years age group. Mumps has an **incubation period** of around 17 days, the extremes being 14–28 days.

Prodromal phase is short (1–2 days) and is characterized by fever, malaise, sore throat, earache and pain behind the ear on chewing or swallowing. **Parotitis**, i.e. tender edematous swelling of parotid (unilateral or bilateral), without involving the submaxillary and sublingual salivary glands, in the subsequent 1–3 days, is the most important development. The enlarged gland displaces the ear lobe upward and outward.

Tenderness and pain subside in 1–3 days, but it takes 7–10 days for the swelling to begin to regress. By this time, fever, anorexia, headache and malaise also disappear. Other glands (like submaxillary and sublingual; Figure 18.7) may also be enlarged. In 10–15% cases, only submandibular glands are to be enlarged.

The opening of the parotid duct, opposite upper second molar is puffy and red. Neurologic involvement in mumps must be borne in mind. One-half of the cases have an asymptomatic CNS involvement. In 1–10% cases, aseptic meningitis or, rarely, encephalitis may occur. Other neurological manifestations include deafness, cerebellar ataxia, GBS, transverse myelitis, facial neuritis, etc. Remaining manifestations include epididymorchitis, pancreatitis with or without insulin dependent diabetes mellitus, myocarditis, oophoritis and nephritis.

Differential Diagnosis

- Other causes of parotid swelling:
 - Suppurative parotitis.



Fig. 18.7: Mumps: Note the swelling of the parotid as well as submaxillary glands.

- Recurrent parotitis secondary to allergy or calculus in Stensen's duct.
- Parotitis from human immunodeficiency virus (HIV), coxsackie A virus, cytomegalovirus, choriomeningitis, etc. in immunocompromised children.
- Lymphadenitis involving preauricular or anterior cervical glands. Mumps requires to be differentiated from cervical lymphadenitis.
- Mikulicz disease (an uncommon condition characterized by involvement of both parotids and lacrimal glands, absence of tears and dryness of mouth), mixed parotid tumor, stone in parotids duct, recurrent parotitis or sarcoidosis, may occasionally need to be excluded.

Diagnosis

Clinical

In the presence of bilateral tender swelling of parotids, especially when reinforced by history of exposure to mumps, diagnosis is clear.

Investigative

When clinical diagnosis requires laboratory backup, the following investigations may be considered:

- Serum amylase—elevated
- Complement fixation test
- ELISA for IgM
- Blood counts reveal leukopenia with lymphocytosis. The first two are of particular value in recognizing mumps meningoencephalitis
- **Cerebrospinal fluid:** High pressure, raised proteins and cells (mostly monocytes).

Complications

Mumps during first trimester of pregnancy may cause intrauterine death, endocardial fibroelastosis and low birth weight (LBW). Box 18.4 lists mumps complications.

Treatment

There is no specific therapy for mumps. General measures are entirely symptomatic and include isolation, rest, antipyretics, local warm or cold applications, saline mouth wash

and, preferably, fluid diet during the initial stages of difficulty in chewing and swallowing. The complications need to be tackled as per the individual merits of each. Many authorities favor the use of corticosteroids in the presence of orchitis.

Prophylaxis

- Active immunization is given in the form of MMR at 15–18 months, See Chapter 10 (Immunization). Some experts do not favor vaccination against mumps. They feel that there is no need for its prevention. Immunization, they argue, may postpone the infection to later age when the disease often runs a severe course.
- Passive protection can be given by convalescent γ -globulin in a dose of 2.5 mL (IM) as soon as possible after exposure.

Prognosis

It is generally good. Most of the children with meningoencephalitis also show complete recovery. Some residual deafness may, however, remain in an occasional case.

ERYTHEMA INFECTIONOSUM

(Fifth Disease)

Usually a benign childhood condition characterized by a classic slapped-cheek appearance and lacy exanthema; it results from infection with human parvovirus (PV) B19, an erythrovirus.

Clinical Features

Prodromal symptoms are mild, begin approximately 1 week after exposure to PV-B19 and last 2–3 days. They include headache, fever, sore throat, pruritus, coryza, abdominal pain and arthralgia. Three phases are given:

- **Phase 1:** The exanthem begins with the classic slapped-cheek appearance (Fig. 18.8A), which typically fades over 2–4 days.
- **Phase 2:** This phase occurs 1–4 days later and is characterized by an erythematous maculopapular rash (Fig. 18.8B) that fades into a classic lacelike reticular pattern as confluent areas clear.
- **Phase 3:** Frequent clearing and recurrences for weeks or occasionally months may occur due to stimuli such as exercise, irritation, stress, or overheating of the skin from sunlight or bathing in hot water.

Diagnosis

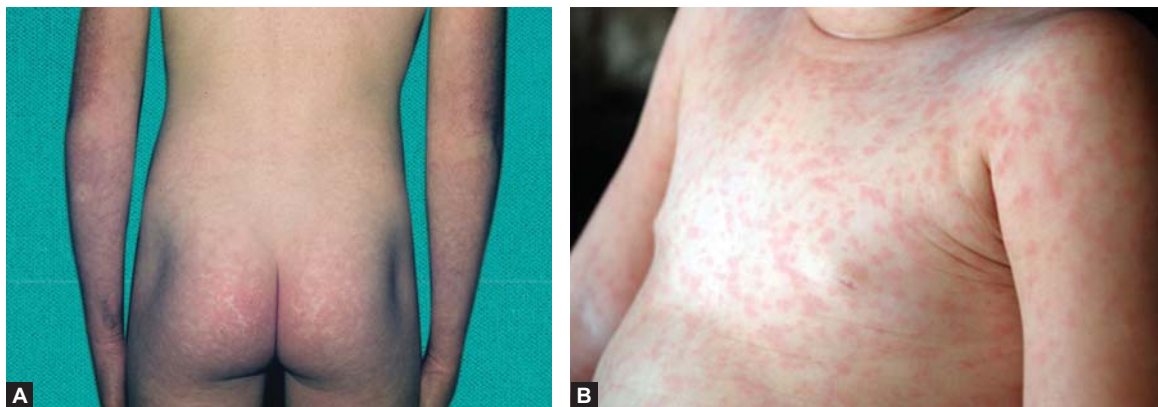
The diagnosis of erythema infectiosum is usually based on clinical presentation alone.

Management

Because erythema infectiosum most often is a benign, self-limited disease, reassuring the parents of children with the condition often is the only intervention necessary. Symptomatic relief of erythema infectiosum may be provided using nonsteroidal anti-inflammatory drugs (NSAIDs) to relieve fever, malaise, headache and arthralgia, along with topical antipruritics and antihistamines (which also relieve pruritus). Treatment also includes plenty of fluids and rest.

Box 18.4 Complications of mumps

- **Orchitis-epididymitis**—quite common and may cause unbearable pain. Its ultimate outcome may be testicular atrophy that can rarely cause sterility. In postpubescent girls, oophoritis may occur
- Pancreatitis is uncommon and shows full recovery in 4–7 days
- Meningoencephalitis, which may precede, accompany or follow mumps, occurs in about 10% of the cases. It is a serious complication and can prove fatal
- Myocarditis, pericarditis, etc
- Nephritis
- Hepatitis
- Thyroiditis
- Mastitis
- Arthritis
- Deafness due to neuritis of auditory nerve
- Facial palsy
- **Ocular**—dacryoadenitis, optic neuritis, uveokeratitis and paresis
- Thrombocytopenic purpura.



Figs 18.8A and B: **Erythema infectiosum**. Note the maculopapular rash over the back and front of the trunk.

ROSEOLA INFANTUM

(Exanthem Subitum, Sixth Disease, Human Herpes Virus 6 and 7)

This benign self-limiting acute measles-like illness with a relatively short course usually occurs in infants and toddlers (6–36 months).

Etiology

It is caused by a DNA virus, human herpes virus-6 (HHV-6). Sometime HHV-7 and echovirus-16 may cause it.

Clinical Features

- **Prodromal phase:** It is characterized by upper respiratory infection (URI) (fever, rhinitis and pharyngitis), conjunctival redness and lymphadenopathy (cervical or occipital). This phase lasts for 3 days.
- **Eruptive phase:** It is characterized a maculopapular rash on trunk followed by face and extremities, lasting 1–3 days. Ulcers (Nagayama spots) may be seen at the uvulo-palatoglossal junction.

Diagnosis

It is by and large clinical.

Differential Diagnosis

It is mainly from other exanthemata, especially measles and rubella and drug hypersensitivity.

Complications

- Febrile seizures
- HHV-6 reactivation in immunocompromised subjects.

Treatment

Supportive care with antipyretics, maintenance of hydration and nutrition.

HAND-FOOT-MOUTH DISEASE

Etiology

This, usually an infectious disease of preschoolers, is caused by Coxsackievirus A16 and enterovirus 71 in most instances. Echovirus and polioviruses can also cause it. Most often, it occurs in epidemic form.



Fig. 18.9: **Hand-foot-mouth disease**. Note the characteristic blisters over palm in a 16-year-old girl.

Clinical Features

- **Prodromal phase:** It is characterized by low-grade fever, sore throat and malaise.
- **Eruptive phase:** It is characterized by formation of blisters and/or ulcers, predominantly over posterior aspect of mouth and a skin rash (papulovesicular) or blisters over hands and feet—mostly on palms and soles (Fig. 18.9).

Diagnosis

By and large on clinical grounds.

Differential Diagnosis

- Other exanthemata, especially varicella
- Herpetic gingivostomatitis
- Aphthous ulcers
- Herpangina.

Complications

Though usually a benign disease, infrequently complications may follow:

- Transient atrophy of nails (a few weeks after the actual infection and recovery from it)
- **Neurological**—flaccid paralysis, encephalitis and aseptic meningitis
- Myocarditis
- Acute respiratory distress syndrome (ARDS).

342 Treatment

Symptomatic with local application of smoothening agents, analgesics and soft food items.

Prevention

- Hand hygiene
- Isolation of index case.

Prognosis

- It is a short-lived infection, resolving in 4–5 days.
- Usually, a self-limited illness with full recovery.

INFECTIOUS MONONUCLEOSIS (Glandular Fever)

Infectious mononucleosis is an acute generalized self-limiting viral infection of the lymphatic system characterized by fever, malaise, sore throat, maculopapular rash, lymphadenopathy, hepatosplenomegaly, atypical lymphocytes in peripheral blood and a heterophil antibody response.

Etiopathogenesis

Epstein-Barr virus (EBV) of the herpes group is the cause of infectious mononucleosis, but other viruses can also cause infectious mononucleosis like disease. EBV is transmitted *via* intimate contact with body secretions, primarily oropharyngeal secretions. However, the virus can also spread through blood and semen during sexual contact, blood transfusions and organ transplantations.

EBV infects the B cells in the oropharyngeal epithelium. Circulating B cells spread the infection throughout the entire RES, i.e. liver, spleen and peripheral lymph nodes, resulting in a humoral and cellular response to the virus.

The humoral immune response directed against viral structural proteins is the basis for the test used to diagnose EBV infectious mononucleosis. However, the T-lymphocyte response is essential in the control of EBV infection and it is critical in determining the clinical expression of EBV viral infection. A rapid and efficient T cell response results in control of the primary EBV infection and lifelong suppression of EBV.

Ineffective T cell response may result in excessive and uncontrolled B cell proliferation, resulting in B-lymphocyte malignancies, e.g. B cell lymphoma.

Epidemiology

It is a common cause of viral pharyngitis in patients of all ages. Most cases of EBV infectious mononucleosis are subclinical, and the only manifestation of EBV infection is positive EBV serological tests. EBV is the main cause of malignant B cell lymphomas in patients receiving organ transplants.

Clinical Features

Incubation period of infectious mononucleosis is 30–50 days. Onset is usually insidious with fever, malaise, extreme

fatigue, headache and sore throat from pharyngitis and tonsillitis. After a week or two, generalized lymphadenopathy and hepatosplenomegaly become apparent. Enlargement of the posterior cervical nodes and epitrochlear nodes is characteristic. Stomatitis with petechiae at junction of hard and soft palate is frequent. An icteric hepatitis is quite common but frank jaundice is infrequent. Rashes and edema of eyelids may occur.

A **maculopapular rash** appearing after administration of ampicillin is a characteristic phenomenon. Occasionally, the child may present with clinical picture suggesting aseptic meningoencephalitis. The disease is self-limiting, the severe manifestations lasting 2–4 weeks followed by gradual recovery.

The term, **chronic mononucleosis syndrome**, refers to persistent EBV infection resulting in a **chronic fatigue syndrome**. It is characterized by an illness starting as infectious mononucleosis and lasting 6 months or more, abnormal EBV antibody profiles, and organ involvement in the form of lymphadenopathy, interstitial pneumonia, hepatitis, splenomegaly or bone marrow hypoplasia. The illness usually affects adolescents (and adults). Similar chronic fatigue syndrome may be caused by human T-lymphotropic virus (HTLV-II), cytomegalovirus (CMV), HHV-6 and some unidentified retroviruses.

Complications

These are listed in Box 18.5.

Diagnosis

Clinical diagnosis may be corroborated by the following investigations:

- **Leucocytosis** of 10,000–20,000 cells/mm³; at least 2/3rd of these are lymphocytes. **Atypical lymphocytes** (large with irregular shape, pale blue vacuolated cytoplasm and eccentric nucleus) form 20–40% of the total lymphocytes.
- **Serologic tests** for heterophil antibodies include Paul-Bunnell test and monospot test. Paul-Bunnell test is based on the observation that numerous abnormal

Box 18.5 Complications of infectious mononucleosis

- Spontaneous splenic rupture, usually in the second week can occur following trauma (as minor as palpation by a doctor)
- Airway obstruction due to massive swelling of tonsils and pharynx may be severe enough to warrant tracheostomy, or, if the condition is duly anticipated, steroids
- Neurologic involvement in the form of convulsions, ataxia and neck stiffness suggesting meningitis, transverse myelitis. Bell palsy, encephalitis, GBS and Alice-in-Wonderland syndrome (meaning perceptual distortion of space and size)
- Myocarditis
- Interstitial pneumonia
- Hepatitis; even Reye syndrome
- Hematogenous involvement in the form of hemolytic anemia, thrombocytopenia, aplastic anemia
- Pancreatitis
- Parotitis
- Orchitis.

Abbreviation: GBS, Guillain-Barré syndrome.

antibodies are found in individuals with this disease. Antibody titer to sheep red cells exceeding 1:28 or 1:40 after absorption with guinea pig cells is regarded positive. Monospot test is quicker, easier and more sensitive and specific than the Paul-Bunnell test.

Differential Diagnosis

- **Atypical lymphocytosis** may necessitate differentiation from CMV infection, infectious hepatitis, toxoplasmosis, typhoid fever, tuberculosis, malaria and mycoplasma infections.
- Occasionally, differentiation may be warranted from streptococcal sore throat (**strep throat**), rubella, mumps and adenovirus disease.
- **Leukemia** becomes an important differential diagnosis when a supposedly infectious mononucleosis patient shows low total leukocytes cells (TLC), moderate thrombocytopenia and hemolytic anemia. Bone marrow is mandatory in this situation.

Treatment

Treatment is supportive and symptomatic. Steroids may be indicated in the following special situations:

- **Short-term:** Pharyngotonsillar edema threatening airway obstruction, hepatitis, abdominal pain due to splenomegaly or lymphadenopathy.
- **Long-term:** Hemolytic anemia and GBS.

The antiviral drug, acyclovir, is of doubtful value in acute infectious mononucleosis. It is, however, beneficial in chronic infectious mononucleosis (as also in EBV-associated polyclonal lymphoproliferation).

Prognosis

In the absence of serious complications, prognosis is uniformly good and the patients eventually recover fully. Following acute illness, fatigue for months, (chronic fatigue syndrome See Chapter 48 (Miscellaneous and Unclassified Issues)) as also recrudescence during the first year is usual.

DENGUE

Dengue is the most common arthropod-borne viral (arboviral) illness in humans. It is caused by infection with 1 of the 4 serotypes of dengue virus, which is a *Flavivirus* (a genus of single-stranded nonsegmented RNA viruses). When a person recovers from dengue infection, he develops long-term (not always lifetime) immunity to that type, but not to the other 3 types. If the person is infected again with a different virus type, he may develop more severe form of the illness known as **dengue hemorrhagic fever** (DHF).

Etiopathogenesis

The causative virus has four antigenic types 1, 2, 3 and 4, belonging to the genus, *Flavivirus*, each producing a similar illness. In our country, all the four types are prevalent. It is spread by the bite of an infected dengue mosquito. There is no spread from human to human. The principle vector involved in transmission of the virus is the mosquito, *Aedes aegypti* (Fig. 18.10) (which is dominant in India) and *Aedes albopictus*.



Fig. 18.10: *Aedes aegypti* mosquito responsible for most case of dengue in India.

Dengue virus transmission follows two general patterns: epidemic dengue and hyperendemic dengue.

1. **Epidemic dengue** transmission occurs when dengue virus is introduced into a region as an isolated event that involves a single viral strain. If the number of vectors and susceptible pediatric and adult hosts is sufficient, explosive transmission can occur, with an infection incidence of 25–50%. Mosquito-control efforts, changes in weather and herd immunity contribute to the control of these epidemics. Transmission appears to begin in urban centers and then spreads to the rest of the country. This is the current pattern of transmission in parts of Africa and South America, areas of Asia where the virus has re-emerged, and small island nations. Travelers to these areas are at increased risk of acquiring dengue during these periods of epidemic transmission.
2. **Hyperendemic dengue** transmission is characterized by the continuous circulation of multiple viral serotypes in an area where a large pool of susceptible hosts and a competent vector (with or without seasonal variation) are constantly present. This is the predominant pattern of global transmission. In areas of hyperendemic dengue, antibody prevalence increases with age, and most adults are immune. Hyperendemic transmission appears to be a major risk for DHF. Travelers to these areas are more likely to be infected than are travelers to areas that experience only epidemic transmission.

Epidemiology

Each year, an estimated 50–100 million cases of dengue fever and 500,000 cases of DHF occur worldwide, with 22,000 deaths (mainly in children). An estimated 2.5–3.0 billion people (approximately 40% of the world's population) in approximately 112 tropical and subtropical countries worldwide are at risk for dengue infection. The only continents that do not experience dengue transmission are Europe and Antarctica. According to the WHO, dengue ranks as the most important mosquito-borne viral disease in the world. In the last 50 years, the incidence of dengue has increased 30-fold worldwide. In India, dengue has been endemic all over the country (Kashmir and Himalayan belt is an exception) since 1963 with periodic extensive epidemics.

344 Currently, DHF is one of the leading causes of hospitalization and death in children in many Southeast Asian countries, with Indonesia reporting the majority of DHF cases. Of interest and significance in prevention and control, three surveillance studies in Asia report an increasing age among infected patients and increasing mortality rate.

WHO's Current Classification

WHO's 2009 classification divides dengue fever into two groups—(1) uncomplicated and (2) severe. This replaces the 1997 WHO classification, which needed to be simplified as it had been found to be too restrictive, though the older classification is still widely used (Fig. 18.11).

Clinical Features

Incubation period is 5–6 days with a variation of 3–15 days. Three phases are—(1) febrile, (2) critical and (3) recovery.

Febrile Phase

Clinical illness begins after a period of 5–6 days (variation 3–15 days) of the bite preceded a day before by viremia which continues till 4–5 days subsequent to the onset of clinical illness. During the course of viremia, the mosquito can get infected following a blood meal on an infected individual. It becomes capable of transmitting the disease to other individuals 8–14 days after the blood meal and remains infective all through its life.

Dengue fever is more commonly seen in older children and adults. It is characterized by abrupt onset of high fever lasting 3–7 days, severe frontal headache, pain behind the eyes and muscle and joint pains. Other symptoms may include loss of appetite, nausea, vomiting and diarrhea, a blanching rash and sometimes minor bleeding (e.g. from nose and gums). The acute symptoms of dengue fever last up to 10 days. Some people may experience repeated episodes

of fever. Full recovery may be slow and associated with weakness and depression. It is rarely fatal. Manifestations include sudden onset of moderate to high fever, headache, retro-orbital pain, muscle, bone and joint pains, anorexia, bad taste in the mouth, and flushing of face. In fair-skinned individuals, a maculopapular rash may be seen over the trunk and upper limbs 3–4 days after the onset of fever, lasting from a few hours to a few days. Often, the fever is biphasic. Convulsions along with tonsillitis, pharyngitis, rhinitis, or diarrhea are encountered in some children. Hemorrhagic manifestations are infrequent.

Positive physical findings may include cervical lymphadenopathy (rarely generalized lymphadenopathy), hepatosplenomegaly and relative or absolute bradycardia.

Critical Phase

Between 3 and 7 days of onset of fever, though fever begins to subside, the child may develop severe manifestations such as bleeding, shock, thrombocytopenia and high hematocrit and even multiorgan dysfunction such as hepatitis, myocarditis and encephalitis.

Recovery Phase

This phase with regression of fever by lysis and profuse sweating in 2–7 days is relatively faster in children. Convalescence is marked by generalized weakness.

Dengue Hemorrhagic Fever (DHF)/ Dengue Shock Syndrome (DSS)

It is a severe, often fatal, form of the disease, is almost exclusively limited to children in some Southeast Asian countries (including India). It is believed to be a hypersensitivity response to a repeat attack with the dengue fever virus. Clinical picture is dominated by fever, hemorrhage and shock. Though hemorrhagic manifestations are usu-

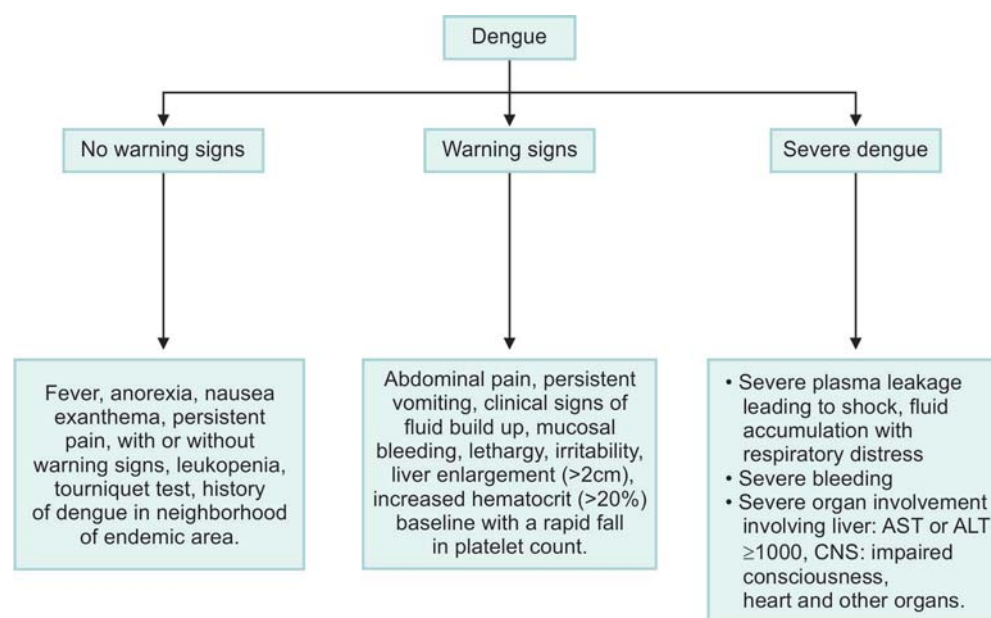


Fig. 18.11: Dengue: World Health Organization classification.

Abbreviations: CNS, central nervous system; AST, aspartate aminotransferase; ALT, alanine transaminase.

ally cutaneous, in the epidemic of DHF/DSS seen by us during fall and autumn of 1993 in Jammu, gastrointestinal hemorrhages dominated the scene.

DHF typically begins with the initial manifestations of dengue fever. The acute febrile illness (temperatures $\leq 40^{\circ}\text{C}$), like that of dengue fever, lasts approximately for 2–7 days. However, in persons with DHF, the fever reappears, giving a biphasic or saddleback fever curve.

Along with biphasic fever, patients with DHF have progressive thrombocytopenia, increasing hematocrit (20% absolute rise from baseline) and low albumin (signs of hemoconcentration preceding shock), more obvious hemorrhagic manifestations (more than 50% of patients have a positive tourniquet test), and progressive effusions (pleural or peritoneal). Lymphocytosis, often with atypical lymphocytes, commonly develops before defervescence or the onset of shock. Transaminase levels may be mildly elevated or present in the several thousands associated with hepatomegaly in those patients with acute hepatitis. Low fibrinogen and elevated fibrin split products are signs of disseminated intravascular coagulation (DIC). Severe metabolic acidosis and circulatory failure can occur.

The critical feature of DHF is plasma leakage. Plasma leakage is caused by increased capillary permeability and may manifest as hemoconcentration, as well as pleural effusion and ascites. Bleeding is caused by capillary fragility and thrombocytopenia and may manifest in various forms, ranging from petechial skin hemorrhages to life-threatening gastrointestinal bleeding.

Liver damage manifests as increase in levels of alanine aminotransferase and aspartate aminotransferase, low albumin levels, and deranged coagulation parameters (prothrombin time, partial thromboplastin time). In persons with fatal dengue hepatitis, infection was demonstrated in more than 90% of hepatocytes and Kupffer cells with minimal cytokine response (tumor necrosis factor {TNF}- α and interleukin {IL}-2).

As the term implies, DSS is essentially DHF with progression into circulatory failure, with ensuing hypotension, narrow pulse pressure (≤ 20 mmHg), and, ultimately, shock and death if left untreated. Death may occur 8–24 hours after onset of signs of circulatory failure. The most common clinical findings in impending shock include hypothermia, abdominal pain, vomiting and restlessness. Box 18.6 gives grading of DHF.

Box 18.6 WHO grading of DHF

- **Grade 1:** Fever, nonspecific constitutional symptoms and positive Hess (tourniquet) test*.
- **Grade 2:** Features of grade 1 + spontaneous bleeding into the skin and/or from other sites.
- **Grade 3:** Circulatory failure manifested by rapid weak pulse, hypotension or low pulse pressure, cold, clammy skin and restlessness.
- **Grade 4:** Profound shock manifested by unrecordable BP and pulse.

Abbreviations: WHO, World Health Organization; DHF, dengue hemorrhagic fever; BP, blood pressure.

* Hess test is considered positive in suspected dengue if petechiae above 20.

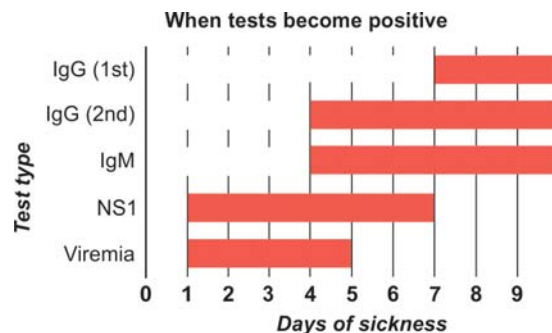


Fig. 18.12: Dengue: Time frame of tests becoming positive.

Abbreviations: Ig, immunoglobulin; NS1, nonstructural protein 1.

Box 18.7 Diagnostic tests for dengue.

Direct methods

- **Culture for virus isolation:** Expensive, not easily workable
- PCR for genome.
- **NS1 antigen:** Based on detection of glycoprotein in initial phase, specificity 100%, sensitivity 90% and 70%, in primary and secondary dengue, respectively.

Indirect methods

Based on antibody determination:

- IgM: More dependable
- IgG: Less useful.

Abbreviations: PCR, polymerase chain reaction; Ig, immunoglobulin; NS1, nonstructural protein 1.

Diagnosis

- Clinical picture of dengue fever is supported by a positive Hess test, raised hematocrit (20% above baseline), leukopenia with relative lymphocytosis, reduced platelet count and increase in immature or unsegmented polymorphonuclear cells (Fig. 18.12).
- Serology and virus isolation are ideal for confirmation of the diagnosis (Box 18.7).

Differential Diagnosis

A large number of conditions, including chikungunya fever, leptospirosis, meningococemia, enteric fever, influenza and malaria need to be considered in the differential diagnosis.

In the event of hemorrhagic manifestations, meningococemia, scrub typhus and leptospirosis become important differential diagnosis. Kyasanur forest disease, yellow fever and hemorrhagic fever with renal syndrome may also need to be borne in mind in certain regions.

Complications

These include:

- Fluid and electrolyte imbalance
- Hyperpyrexia
- Shock
- Febrile seizures.

Treatment

There is no specific treatment whatsoever for dengue fever. Management is more or less supportive and consists of:

- Controlling high fever with hydrotherapy/antipyretics (paracetamol; no aspirin; avoid NSAIDs)

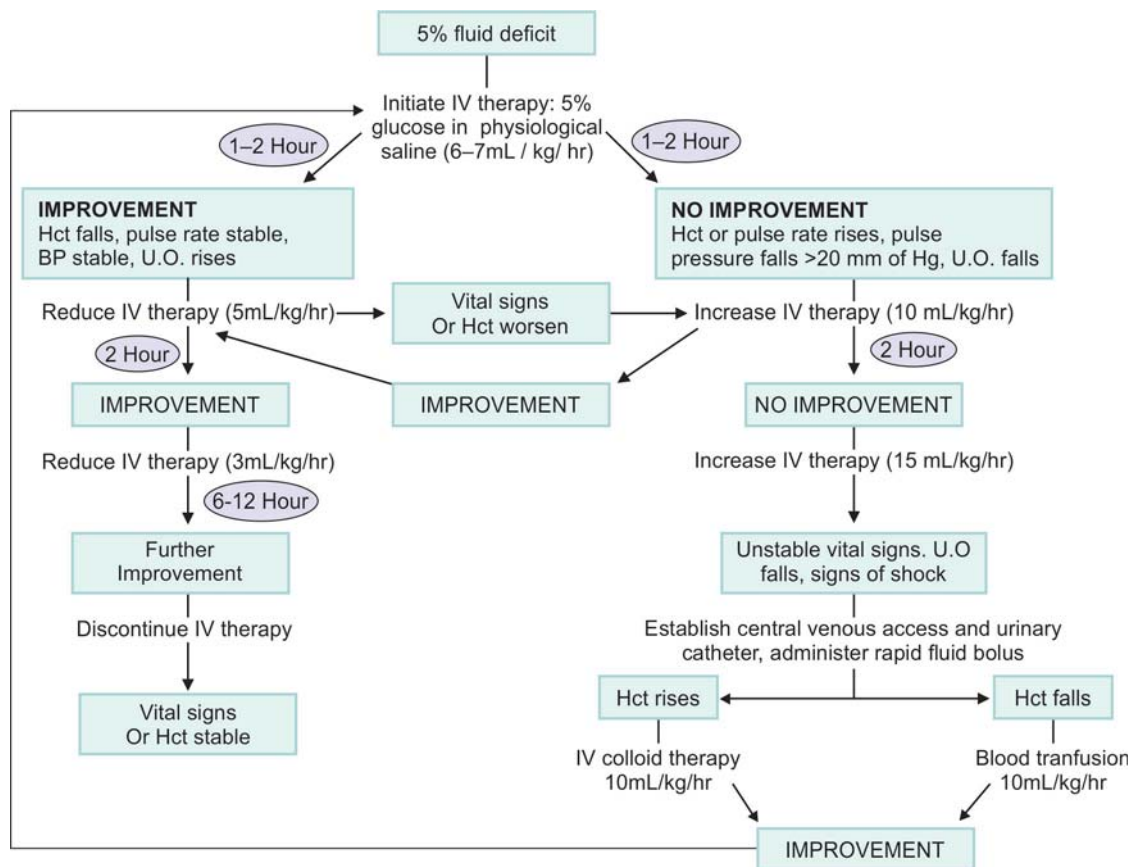


Fig. 18.13: Severe dengue (dengue hemorrhagic fever {DHF}). Volume replacement flowchart for a patient with DHF and more than 20% increase in Hct. Abbreviations: Hct, hematocrit; IV, intravenous; U.O, urine output.

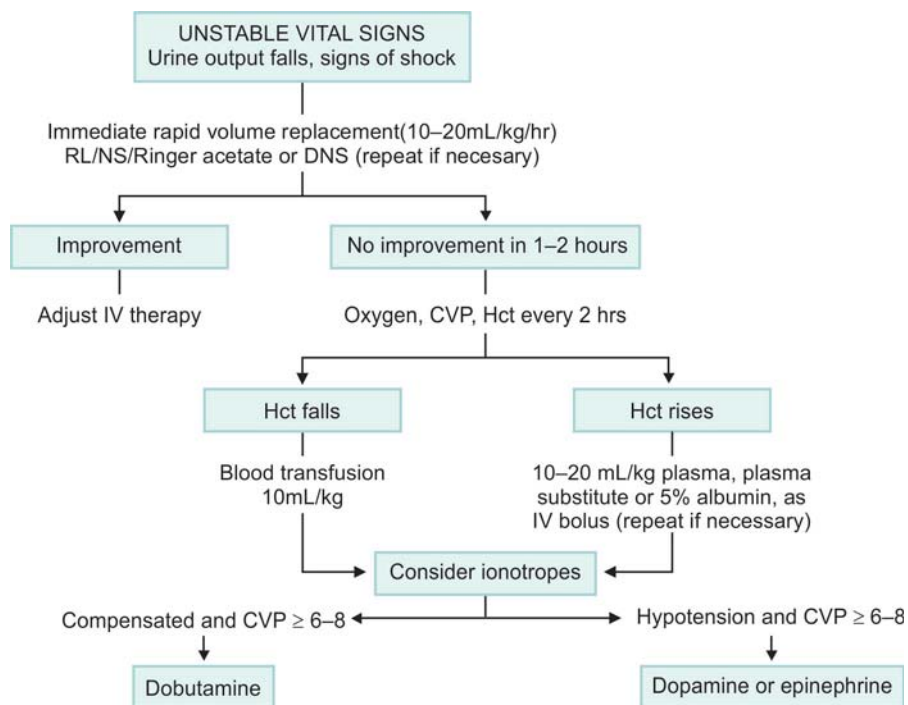


Fig. 18.14: Severe dengue (dengue shock syndrome {DSS}). Volume replacement flowchart for a patient with DSS. Abbreviations: Hct, hematocrit; CVP, central venous pressure; DNS dextrose normal saline; RL, ringer lactate; NS normal saline.

- Relieving pains with analgesics
- Maintenance of fluid and electrolyte balance and nutrition (Figs 18.13 and 18.14)
- Monitoring of the vital signs
- Fresh blood transfusion in case of accompanying bleeding manifestations
- In established thrombocytopenia, transfusion of a platelet concentrate, 10 mL/kg, to raise the platelet

count to above 50,000/mm³, is strongly recommended. The concentrate can be prepared either by centrifugation of fresh whole blood or by automated platelet pheresis. Multiple platelet transfusion may lead to platelet refractoriness. Hence, multiple platelet transfusion must employ filtered (leukocyte-reduced) platelet concentrates. Moreover, platelet concentrates must be infused within 2 hours (maximum).

Monitoring

Close monitoring of the patient is quite critical especially in first few hours. Vitals need to be measured every 30 minutes till they stabilize and thereafter every 2 hours. Central venous monitoring should be done in children with features of shock. Hematocrit needs to be measured every 2 hourly for first 6 hours or until stable. Platelets are done daily till they show a rising trend.

Discharge Criteria

Patients with DHF or DSS may be discharged from the hospital when they meet the following criteria:

- Afebrile for 24 hours without antipyretics
- Good appetite, clinically improved condition
- Adequate urine output
- Stable hematocrit level
- At least 48 hours since recovery from shock
- No respiratory distress
- Platelet count greater than 50,000 cells/ μ L.

Prognosis

Dengue fever is usually self-limited and benign. If complications are prevented or handled well, full recovery is a rule. If left untreated, the mortality in patients with DHF or DSS may be as high as 40–50%. Early recognition, careful monitoring and appropriate fluid therapy has resulted in mortality rate of 1–5%. Prognosis is poor in patients with prolonged shock. So, early recognition of shock is of paramount importance.

Prevention

- **Antimosquito measures:** A wholesale attack on the vector mosquito (*Aedes aegypti*) population and personal protective measures are needed. Growing shellfish in ponds and water traps assists in eliminating larvae of the vector.
- **Dengue vaccine:** A killed vaccine for dengue fever, though effective in prophylaxis, is not easily available. Attenuated dengue types 1, 2 and 4 vaccines are being developed in Thailand. A possible risk of dengue vaccination is sensitization of the recipient, resulting in predisposition to severe dengue (DHF) after a subsequent dengue infection.

CHIKUNGUNYA

Definition

Chikungunya, an acute re-emerging disease caused by chikungunya virus (CHIKV), is characterized by fever,

arthritis and skin rash. The name *chikungunya* translates to that which bends up in the Makonde dialect of Tanzania, describing the physical appearance of a patient with severe clinical features.

Etiology

Chikungunya fever is caused by a single-stranded RNA alphavirus (CHIKV) from the family *Togaviridae* which is transmitted by mosquitoes, *Aedes*, *Culex* and *Mansonia*. The most common vector involved in transmission is infected *A. aegypti* mosquito and less commonly by the *A. albopictus*.

Epidemiology

It was in 1952–1953 that this virus was first isolated in Tanzania from patients and mosquitoes. Two outbreaks of chikungunya, in Kolkata in 1963–1964 and in Chennai in 1965, are on record. Having remained dormant for three decades, the virus has become active in recent years, giving rise to hundreds of cases of chikungunya in South India in particular. More than 1.25 million cases of chikungunya fever have been reported in India, mainly in the Karnataka and Maharashtra provinces. There is a significant risk of importation of CHIKV to nonendemic countries worldwide due to the high viremia of infected individuals and expansive distribution of both *A. aegypti* and *A. albopictus*. Autochthonous transmission has also been documented in a limited area in Italy when an infected traveler transmitted the virus to local *A. albopictus*. For travelers, risk is highest in endemic areas during the rainy season, when the density of the vector is highest.

Clinical Features

Incubation period is 2–12 days. The onset is acute with fever, headache, fatigue, nausea, muscle pain, rash and pain in joints. Fever is often accompanied by rigors. The acute phase last for 2–3 days which is followed by joint pain which is very severe, is polyarticular, migratory and affecting mainly the small joints of hand and wrist, ankle and feet. Large joints are less involved. An itchy, transient maculopapular rash appears 4–8 days later over trunks and limbs. Inguinal lymphadenopathy may occur. The joint pains may persist for many months after the acute illness.

Diagnosis

Chikungunya should be suspected in any patients presenting with a triad of fever, rash and joint pain/arthritis. Investigations include:

- Polymerase chain reaction (PCR) can be used to detect the virus during acute phase.
- Viral specific IgM antibodies may be detected by capture.
- ELISA and hemagglutination inhibition assays during 5–7 days of illness.

Treatment

Currently, no specific treatment is available for chikungunya fever, although various antiviral agents are being investigated. Treatment is mainly supportive in the form of:

- 348 ■ Rest
 ■ Fluids
 ■ Paracetamol and NSAIDs.

Prevention and Control

- **Antimosquito measures:** The best prevention is to avoid mosquito bites with proper insect precautions. To limit further transmission of the virus, patients should be kept under mosquito netting while febrile.
- **Vector control:** It is targeted at *A. aegypti* mosquito and comprises keeping breeding places of mosquitoes such as water containers and air coolers free of mosquitoes and use of insecticides and aerosol of ultra-low volumes of malathion or sumithion.
- **Vaccination:** A suitable vaccine is not yet available.

JAPANESE ENCEPHALITIS

Japanese encephalitis (JE) is a mosquito-borne viral encephalitis which is endemic in many regions of India, especially Bihar and the adjoining states.

Etiology

It was primarily a zoonotic disease, JE is mosquito-borne encephalitis caused by group B arbovirus (Flavivirus) and transmitted by bite of culicine mosquitoes (Vector of JE) as shown in Figure 18.15. The virus is particularly common in areas where rice cultivation occurs. The irrigated rice fields attract the natural avian vertebrate hosts and are breeding sites for mosquitoes such as *Culex tritaeniorhynchus*.

Clinical Features

Incubation period is 5–15 days. A large majority of the cases have an inapparent infection. Full-blown disease shows three stages:

1. **Prodromal stage:** It is characterized by fever, headache and malaise, lasting for 1–6 days.
2. **Acute encephalitic stage:** It is characterized by high fever, neck rigidity, seizures, change in sensorium (even coma) and focal neurologic signs.
3. **Late stage (sequelae):** It is characterized by resolution of active inflammation (resulting in control of fever, and erythrocyte sedimentation rate reverting to normal), CNS signs becoming stationary or showing improvement. Residual neurologic deficit (sequelae) may remain.

Management

It is by and large supportive.

Prognosis

Mortality is high, usually varying from 20% to 40%. On an average, death occurs after 7 days of onset of disease.

Prevention/Control

- **Vector control:** Mosquito nets, aerial/ground fogging with fenitrothion or malathion
- **Vaccination:** See Chapter 10 (Immunization).

RABIES

(Hydrophobia)

It is an acute, fatal viral infection of the CNS resulting from contamination of a wound with saliva of rabid animal, usually a stray dog.

Etiology

Rabies virus is a neurotropic bullet-shaped, RNA virus, consists of Negri bodies, which are observed in the cytoplasm

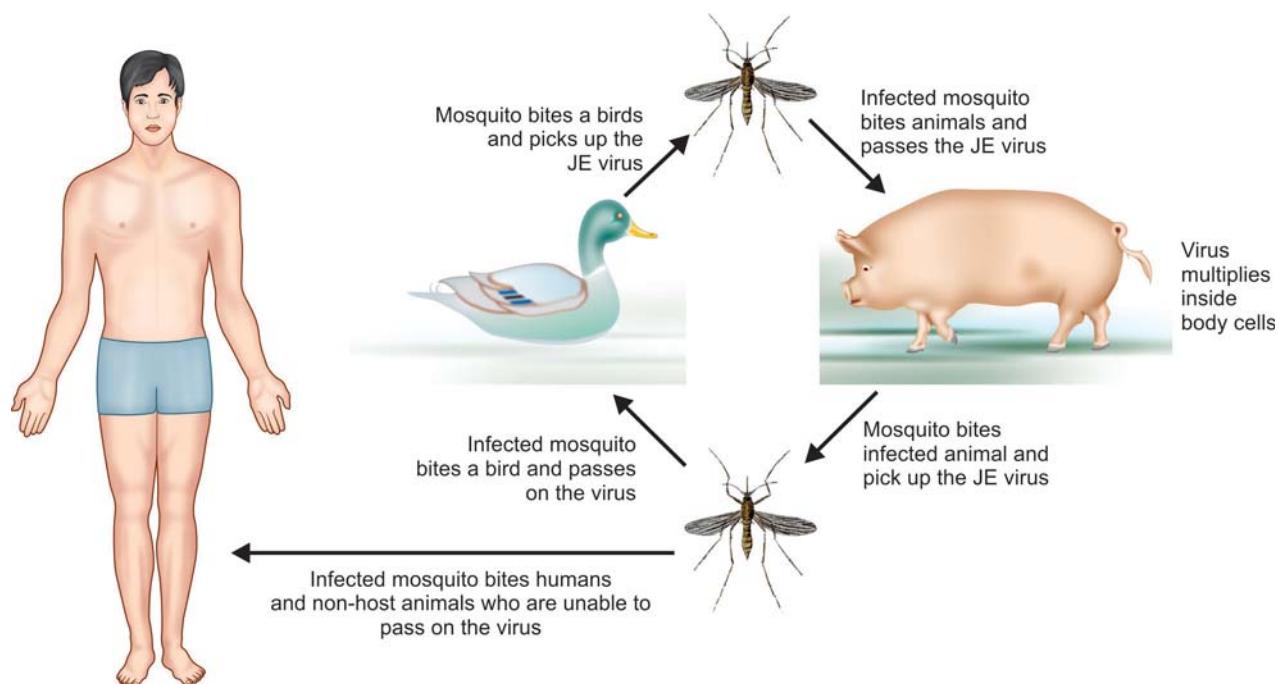


Fig. 18.15: Japanese encephalitis (JE). Note the life cycle of the JE virus.

of infected neurons. The source of infection to man is mainly saliva of rabid animals. In dogs and cats, the virus may be present in saliva for 3–4 days before the onset of clinical illness till death. The domestic animals like cow, buffalo, goat, pig and sheep can transmit rabies after they are bitten and get infected by rabid animals.

Common modes of transmission are bites and scratch from infected animals; lick on broken skin/intact or broken mucus membrane. Transmission via aerosol or organ transplantation (cornea, liver, kidney from persons dying from unspecified encephalitis) is rare. Man to man transmission is also possible. Transmission rate is increased if the victim has suffered multiple bites and inoculation occurs in highly innervated parts of the body such as the face, neck, hands and incubation period will be shorter here.

Pathogenesis

The virus replicates in muscle or connective tissue cells at the site of entry. It then attaches to nerve endings and ultimately enters peripheral nerves. It spreads centripetally via the peripheral nerves toward the CNS. Following infection of the CNS, the virus spreads to skeletal and myocardial muscle, adrenal glands and skin. Spread to salivary glands is important for further transmission of the virus to another host. The pathologic hallmark of rabies is the Negri body that is found in neurons.

Neuronal destruction in the brainstem and medulla with most severe changes in pons and fourth ventricle is the basic lesion. The disease is brainstem encephalitis with intact cortex and maintenance of sensorium.

Epidemiology

Rabies is more prevalent in the developing world than in industrialized countries. The WHO estimates that rabies is responsible for 35,000–50,000 deaths annually worldwide.

Clinical Features

Incubation period of rabies in man varies from 20 days to 180 days; peak 1–3 months. In some cases, symptoms first occur within 5 days after exposure. Although all age groups are susceptible, rabies is most common in children less than 5 years. There are two clinical forms of rabies:

1. **Encephalitic or furious rabies:** It constitutes 80% of rabies illness and starts with nonspecific symptoms including fever, sore throat, malaise, headache, nausea, vomiting and abnormal sensation at the site of bite. Following this, patient develops agitation, hyperactivity, restlessness, thrashing, biting, confusion, or hallucinations. After several hours to days, this becomes episodic and interspersed with calm, cooperative, lucid periods. Furious episodes last less than 5 minutes. Episodes may be triggered by visual, auditory, or tactile stimuli or may be spontaneous. Seizures may occur. Development of hydrophobia and aerophobia is pathognomonic of furious rabies, which is demonstrated by asking the patient to drink or by fanning air over the face. This is due to spasms of muscles of larynx, neck and chest wall. This

phase may end in cardiorespiratory arrest and death within 10 days of onset or may progress to paralysis. **349**

2. **Paralytic or dumb rabies:** It is the less frequent form and constitutes 20% of rabies cases. It is characterized by ascending motor weakness involving limbs and cranial nerves. In patients with paralytic rabies, fever and nuchal rigidity may occur. Paralysis is symmetrical and may be either generalized or ascending and may be mistaken for GBS. The sensory system is usually spared. Calm clarity gradually progresses to delirium, stupor, and then coma. Death occurs in 7–21 days.

Diagnosis

Diagnosis is mainly based on the history of bite by a rabid animal or any other animal bite (unprovoked) and characteristic clinical picture. It is confirmed in patients early in illness by antigen detection using immunofluorescence of skin biopsy, and by virus isolation from saliva and other secretions. Antibody detection in CSF is considered diagnostic of rabies, irrespective of immunization status.

Differential Diagnosis

Other infectious causes of encephalitis, transverse myelitis, cerebrovascular accident, psychosis, intracranial mass, epilepsy, atropine poisoning, Creutzfeldt-Jacob disease, poisoning with atropine like compounds, pseudohydrophobia (hysterical reaction to animal bites due to fear of rabies).

Treatment

There is no specific treatment available. It is uniformly fatal and antivirals have no role to play. Rabies Ig or rabies vaccine does not alter the course of disease once symptoms have appeared.

Case management comprises of isolating patient in a quiet room, protected as far as possible from external stimuli such as bright light, noise, cold air which may precipitate spasms or convulsions. Maintaining vitals, relieving anxiety and pain with sedatives and proper hydration are of utmost importance. Intensive therapy in the form of respiratory and cardiac support may be given, but has not much impact on the final outcome of the disease.

Prevention

Since dog is the major source of infection, the most cost-effective approach in rabies control is elimination of stray and ownerless dogs, combined with prophylactic vaccinations of dogs. Animal birth control-antirabies (ABC-AR) program is in action in India for this purpose. Avoidance of contact with potentially rabid animal and proper disposal of infectious secretions of a patient of rabies are also crucial.

Post-exposure Prophylaxis

All human exposure should be treated as a medical emergency. Combination of antirabies serum with a course of vaccine, together with local treatment of the wound is the best measure after exposure of the child to rabies. Further details are available in Chapter 10 (Immunization).

350 Pre-exposure Prophylaxis

As rabies is a very fatal disease and young are at risk for getting the infection, it may be beneficial if we vaccinate them before attaining 3 years, when they start outdoor activity. Cell culture vaccine is given in 3 doses IM on day 0, 7 and 28.

PEDIATRIC ACQUIRED IMMUNE DEFICIENCY SYNDROME

(HIV Infection)

Acquired immunodeficiency syndrome (AIDS), aptly described as the **20th century plague**, and **worst among the most devastating diseases of the day**, is characterized by total collapse of the immune system of the body, rendering the subject acutely vulnerable to opportunistic infections that eventually prove fatal; even a minor common cold.

Etiological Virus

Human immunodeficiency viruses (HIV-1 and HIV-2) belong to the Retroviridae family and *Lentivirus* genus. Almost always, it is HIV-1 that causes AIDS in children.

Epidemiology

In children, dominant route of transmission is vertical from mother to child during intrauterine or intrapartum periods or through breastfeeding. Risk factors are listed in Box 18.8.

Generally, AIDS in newborns is perinatally acquired though in utero as well as postnatal infection from breast milk can occur. A strong link has been documented between maternal vitamin A deficiency and vertical transmission of HIV, increasing the risk by 3 to 4 folds.

Pathogenesis

Acquired immunodeficiency syndrome produces disturbance in all the four major components of the normal immune system, namely T cells, B cells, complement and phagocytic activity. The most prominent effect is on the T cells, resulting in reversal of helper/suppressor T cell ratio (the normal being over 1.0), which tends to persist. With progression of the disease, such functional abnormalities of the T cells as abnormal response of lymphocytes to antigens, mitogens and allogeneic cells and failure to produce normal amounts of IL-2, interferon and other lymphokines may result.

Box 18.8 Risk factors for pediatric HIV/AIDS.

- Mothers who are addicted to intravenous drug(s)
- Mothers who indulge in prostitution
- Mothers who are heterosexual with bisexual husbands
- A history of blood transfusion with blood or its products including factor VIII concentrates within the preceding 5 years
- A history of residence in certain geographical areas that are inhabited considerably with AIDS patients.

Abbreviations: HIV, human immunodeficiency virus, AIDS, acquired immunodeficiency syndrome.

T cell defect leads to defect in B cell system, resulting in polyclonal hypergammaglobulinemia (raised IgA, IgG and IgM). Consequent upon this, the patient fails to form antibodies to antigens with which he has recently been immunized.

An increased amount of circulating immune complexes due to chronic microbial infections is a rule. Some subjects show abnormal monocyte chemotaxis, antigen processing and cytotoxicity.

Leading causes of mortality are opportunistic infections and Kaposi sarcoma and other malignancies. Classical histologic feature of pediatric AIDS is wide-spread lymphoid infiltration of the lung, the so-called **diffuse lymphoid interstitial pneumonia**. Thymus and lymphoid tissue show histologic features of a chronic infection. The entire tissue appears to be made up of cords and broad sinuses.

Clinical Features

Incubation period (time from exposure to the virus to the development of the disease) varies between 3 months and 5 years, depending on a pre-existing immunodeficiency such as prematurity or viral immunosuppression, or presence of other infections.

Manifestations in infants born to mothers with risk factors include small for dates, failure to thrive, microcephaly, hepatosplenomegaly, lymphadenopathy, chronic interstitial pneumonia—*Pneumocystis carinii* (*P. jiroveci*), recurrent otitis media, chronic sinopulmonary infection, oral candidiasis, chronic diarrhea and chronic parotid swelling. Kaposi sarcoma is uncommon in pediatric AIDS.

Manifestations of transfusion-associated AIDS include *P. jiroveci* pneumonia, Kaposi's sarcoma, chronic lymphadenopathy with recurrent pyrexia, night sweats, weight loss, chronic diarrhea, hepatosplenomegaly and evidence of other viral infections like EBV, hepatitis B and CMV. Box 18.9 lists the clinical features of pediatric AIDS.

Diagnosis

The following factors, if present, are considered sufficient to reach the diagnosis of AIDS in infants and children.

- A risk factor associated with AIDS
- Polyclonal hypergammaglobulinemia
- T cell immunodeficiency
- Evidence of infection with HIV.

Investigations suggested for a suspected case of AIDS are:

- TLC and differential leukocyte count (DLC) lymphopenia (under 2,000/mm³) is a significant finding
- Platelet count indicating thrombocytopenia
- Quantitative measurement of immunoglobulin levels to substantiate the raised levels of IgA, IgG and IgM
- Demonstration of a reduced helper/suppressor T cell ratio
- Circulating immunocomplexes
- Reduced IL-2 and interferon
- Reduced natural killer cells
- Lymph node biopsy
- ELISA test

Box 18.9 Clinical features of pediatric AIDS**Generalized (Nonspecific) pyrexia**

- FTT
- Lymphadenopathy
- Recurrent infections
- Developmental delay
- LBW

Specific

- Embryopathy
- Microcephaly
- Facial dysmorphism
- Hepatosplenomegaly
- Lymphocytic interstitial pneumonia
- Diarrhea
- Gastrointestinal bleeding
- Cardiomyopathy
- Arteriopathy
- Nephropathy
- Encephalopathy
- Parotitis
- Kaposi sarcoma
- Rashes

Infections

- *Pneumocystis carinii*
- *Cryptosporidium*
- *Cryptococcus*
- *Moniliasis*
- CMV
- EBV
- Herpes simplex (type 1 and 2)
- Varicella zoster
- *Hemophilus influenzae* (type B)
- *Pneumococcus*
- *Salmonella*
- *Shigella*
- *Lamblia giardia*
- *Entamoeba histolytica*.

Abbreviations: FTT, failure to thrive; LBW, low birth weight; CMV, cytomegalovirus; EBV; Epstein-Barr virus; AIDS, acquired immunodeficiency syndrome.

- Western blot test
- Culture of the virus
- T cell growth factors.

If *P. carinii* (*P. jiroveci*) pneumonitis is suspected, demonstration of the causative organisms, *P. carinii* may be done on bronchoalveolar lavage, tracheal aspirate, transbronchial lung biopsy, bronchial brushings, percutaneous transthoracic needle aspiration, induced sputum samples, or open lung biopsy, the last-named being the most reliable method. Box 18.10 gives diagnostic criteria of AIDS and Box 18.11 gives classification of HIV infection in children.

Management

The patients with risk factors associated with AIDS, especially the mothers, must be advised to appreciate that they or their offsprings may be heading for a potentially fatal disease and that they must change the lifestyle.

Reducing exposure to the offending virus is a must; say by instituting screening measures to exclude blood donors and individuals with AIDS-associated risk factors. Attempts to inactivate retrovirus in factor VIII concentrate to cut down the risk of AIDS to hemophiliacs are in

Box 18.10 WHO criteria for diagnosis of pediatric AIDS in developing countries such as India**Major criteria**

- Weight loss or abnormally slow growth
- Chronic diarrhea for over 1 month
- Prolonged or intermittent pyrexia for over 1 month

Minor criteria

- Generalized lymphadenopathy
- Oropharyngeal candidiasis
- Recurrent common bacterial infections
- Persistent cough for over 1 month
- Generalized dermatitis
- Confirmed HIV infection in the mother.

Note: The existence of 2 major and 2 minor criteria in the absence of other known causes of immunodeficiency is diagnostic of AIDS.

Abbreviations: WHO, World Health Organization; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Box 18.11 Classification of HIV infection in children under 13 years as per the CDC**Class P-0**

Intermediate infection in infants under 15 months of age (who are exposed to an infected mother) with antibodies to HIV.

Class P-1• **Asymptomatic infection:**

- Subclass A: Normal immune function
- Subclass B: Abnormal immune function
- Subclass C: Immune function remains untested

Class P-2• **Symptomatic infection:**

- Subclass A: Nonspecific findings
- Subclass B: Progressive neurologic disease
- Subclass C: LIP established by chest X-ray or histopathologically.
- Subclass D: Secondary infectious diseases.
- Subclass E: Secondary malignancies
- Subclass F: Other diseases possibly due to HIV infection, including cardiomyopathy, hepatitis, nephropathy, hematologic and dermatologic disorders.

Abbreviations: HIV, human immunodeficiency virus; CDC, center disease control and prevention; LIP, Lymphocytic interstitial pneumonitis.

progress. A desperate search for an effective AIDS vaccine is in progress.

Zidovudine is of value for decreasing perinatal transmission of HIV. Boxes 18.12 to 18.14 give the lists of available antiretroviral drugs along with their dosage. Instead of the monotherapy, the current recommendation is for combination therapy, in the form of highly active antiretroviral therapy (HAART) which consists of a combination of two nucleoside reverse transcription inhibitors (NRTIs) and a protease inhibitor (Box 18.15).

Supportive measures include:

- Pentamidine and cotrimoxazole for *P. carinii* infection
- Strong antifungal agents like ketoconazole and amphotericin B for chronic candidiasis.
- IV γ -globulin, 100–200 mg/kg every month, for prevention of bacterial and viral infections.
- Irradiation of all blood products to be transfused to prevent graft vs host reaction, and ensuring absence of antibodies against cytomegalovirus in them.
- Avoidance of immunization, etc.

Box 18.12 Recommended nucleoside with pediatric dosage**Zidovudine (ZDV, AZT)**

- Dose: Newborn: 4 mg/kg BID
 - 3 months–13 years: 90–180 mg/m² (maximum 200 mg) q 6–8 hourly
 - More than 13 years: 300 mg q 12 hourly
- ADRs: Anemia, rash, hepatotoxicity with hepatomegaly, myopathy and seizures

Lamivudine (3TC)

- Dose: 1 month–13 years: 4 mg/kg BID
 - Less than 13 years but weight <50 kg: 4 mg/kg/dose q 12 hourly
 - Less than 13 years but weight >50 kg: 150 mg/dose q 12 hourly
- ADRs: Anemia, neutropenia, thrombocytopenia, raised pancreatic enzymes/pancreatitis and raised liver enzymes

Didanosine

- Dose: 0–3 months: 50 mg/m²
 - 3 months–13 years: 90–150 mg/m² (maximum 200 mg), q 12 hourly
 - 13 years but weight <60 kg: 125 mg q 12 hourly
 - 13 years but weight >60 kg: 200 mg q 12 hourly
- ADRs: Abdominal discomfort, diarrhea, raised pancreatic enzymes/pancreatitis, raised liver enzymes and peripheral neuropathy

Stavudine (d4D)

- Dose: 1 month–13 years: 1 mg/kg 12 hourly
 - 13 years but weight 30–60 kg: 30 mg/dose q 12 hourly
 - 13 years but weight >60 kg: 40 mg/dose q 12 hourly
- ADRs: GI upset, headache, neuropathy, raised pancreatic enzymes/pancreatitis and raised liver enzymes

Abacavir (ABC)

- Dose:
 - 3 months–13 years: 8 mg/kg q 12 hourly
 - More than 13 years: 300 mg (maximum) q 12 hourly
- ADRs: Hypersensitivity, GI upset, lethargy, drowsiness, head-ache and cough

Zalcitabine

- Dose:
 - Less than 13 years: 0.01 mg/kg 8 hourly
 - 13 years: 0.75 mg q 8 hourly.

Abbreviations: ADR, adverse drug reaction; GI, gastrointestinal.

Box 18.13 Recommended non-nucleoside reverse RTIs**Nevirapine (NVP)**

- Dose: 2 months–13 years:
 - 120–200 mg/m² q 12 hourly × 2 weeks.
 - Follow with 150–200 mg/m² q 12 hourly
 - 13 years: 200 mg q 24 hourly × 2 weeks
 - Follow with an increase to 200 mg q 12 hourly (provided no SADR occurs)

Efavirenz (EFV)

- Dose: >3 years: 200–600 mg OD depending on weight
- ADRs: Rash, GI upset, headache, fatigue, raised liver enzymes and neuropathy

Delavirdine (DLV)

- Dose: 400 mg TDS (adolescents).

Abbreviations: RTI, reverse transcription inhibitors; GI, gastrointestinal; TDS, thrice a day; ADRs, adverse drug reactions; SADR, severe adverse drug reaction.

Use of bone marrow transplantation, thymic factors and interleukin for correcting the immunologic defects in AIDS has proved to be of no value.

Prognosis

HIV infected children now live longer with improved quality of life. Two most important prognostic indicators are:

Box 18.14 Recommended protease inhibitors**Ritonavir (RTV)**

- Dose:
 - Less than 13 years: 350–400 mg/m² 12 hourly
 - Start with only 250 mg/m²
- ADRs: GI upset, bad taste

Nelfinavir (NFV)

- Dose: Less than 13 years: 50–55 mg/kg q 12 hourly
- ADRs: GI upset, including abdominal discomfort, rash, diabetes, hyperlipidemia and hepatitis

Amprenavir

- Dose:
 - 4–16 years but (<50 kg): 225 mg/kg q 12 hourly
 - 13 years but (>50 kg): 1200 mg q 12 hourly
- ADRs: GI upset

Indinavir

- Dose:
 - Less than 13 years: 500 mg/m² q 8 hourly
 - 13 years: 80–100 mg q 8 hourly
- ADRs: Renal stones and jaundice

Nelfinavir

- Dose:
 - Less than 13 years: 50–60 mg q 12 hourly
 - 13 years: 1250 mg q 12 hourly
- ADRs: GI upset

Lopinavir (LPV)

- Dose:
 - 6 months–12 years:
 - 7–15 kg 12 mg/kg
 - 15–40 kg 10 mg/kg
 - 12 years: 400 mg
- ADRs: GI upset, headache, raised lipids

Saquinavir

- Dose: 50 mg/kg q 8 hourly
- ADRs: GI upset, rash, headache.

Abbreviations: ADRs, adverse drug reactions; GI, gastrointestinal.

Box 18.15 Highly active antiretroviral therapy (HAART)**2 NRTI choices**

- ZDV + ddI
- ZDV + 3TC
- D4T + ddI
- D4T + 3TC

Third drug (Protease inhibitor)

- RTV/NFV (liquid formulation)
- NFV/IDV/Saquinavir (tablet/capsule form)

Note: HAART consists of a combination of 2 NRTIs and a protease inhibitor.

Abbreviations: NRTI, nucleoside reverse transcriptase inhibitors; NFV, nelfinavir; IDV, indinavir; RTV, ritonavir; ddI, didanosine; ZDV, zidovudine.

1. **Plasma viral load:** Higher the viral load, greater is the risk of disease progression.
2. **CD4 lymphocyte percentage:** Mortality rate is higher in patients with CD4 lymphocyte percentage less than 15%. Prognosis is worst in children with osteogenesis imperfecta, encephalopathy, or wasting syndrome. Children with lymphadenopathy, splenomegaly, hepatomegaly, lymphoid interstitial pneumonia and parotitis have relatively better prognosis.

Special Issues in Pediatric HIV/AIDS

Prevention of Vertical Transmission to Baby

It has already been in detailed in Chapter 12 (Infant and Young Child Feeding).

Breastfeeding

If the mother satisfies the specific criteria for artificial feeding in the form of affordability, feasibility, availability, sustainability and safety (AFASS), exclusive artificial feeding (not the mixed feeding) is the recommended modality of feeding during the first 6 months of life.

Else, artificial feeding is the recommendation. There is evidence that exclusively breastfeeding (EBF) carries lower risk of HIV transmission than mixed feeding. For details, See Chapter 12 (Infant and Young Child Feeding).

Immunization

- Asymptomatic subjects can receive all vaccines.
- Symptomatic subjects should not be given live vaccines (Bacillus Calmette-Guerin {BCG}, measles, MMR, oral typhoid) except when CD⁴ count is >15% for the age.
- Infants born to HIV-positive mother, but with indeterminate HIV status should be vaccinated as normal infants.
- Hepatitis B needs to be given in double the dose and for 4 doses for achieving acceptable seroconversion. Also, See Chapter 10 (Immunization).

HIV/AIDS and Tuberculosis

HIV/AIDS have adverse influence on tuberculosis, enhancing the risk of development of multidrug resistant (MDR) strains.

RESPIRATORY SYNCYTIAL VIRUS INFECTION

Respiratory syncytial virus (RSV), a pneumovirus, is a single-stranded RNA virus, with a lipid bilayered envelope. The envelope secretes a special protein, transmembrane protein F that contributes to formation of syncytia, i.e. the epithelial cells of the respiratory tract.

Epidemiology

Contrary to the general belief that RSV infection is a problem of the West, WHO has shown that even in the developing countries RSV is the main cause of lower respiratory tract infection (LRTI), killing around 600,000 infants and young children annually.

Risk Factors

Recognized risk factors for development of severe RSV infection include:

- Prematurity
- Chronic lung disease
- Congenital heart disease
- Immunocompromised state and
- Age under 6 weeks.

Clinical problems resulting from RSV infection include acute bronchiolitis and viral pneumonia.

Diagnosis

It is usually clinical. Definitive diagnosis is by demonstration of the RSV or its antigen in the respiratory secretions, usually from posterior nasal cavity, nasopharynx or throat.

Treatment

The only recognized antiviral drug for RSV infection is ribavirin aerosol which should be administered early in the course of the disease in very sick or high-risk infants. Also See Chapter 21 (Protozoal Infections and Infestations).

Prophylaxis

Prophylaxis in high-risk subjects is possible through:

- Respiratory syncytial virus immune globulin (RSVIG)
- A humanized anti-RSV monoclonal antibody (Palivizumab).

A suitable vaccine for use in infants and children, though urgently needed, is yet to be available.

INFLUENZA (Flu)

A viral illness usually occurring in winter months year after year (seasonal influenza) or as pandemic every 30–40 years (pandemic influenza). Only recently (2009–2010), the world had Novel H1N1 pandemic. In India and many other countries of tropics and subtropics, influenza occurs all through the year rather than restricting itself to autumn of winter months.

Usually, in healthy subjects, influenza has a benign course, resolving in 1–2 weeks. In certain situations such as immunocompromised subjects, underlying heart disease, pulmonary disease (asthma, cystic fibrosis), obesity, etc., the subjects are vulnerable to complications. Extremes of life (children and elderly subjects more than 65 years of age) and pregnancy are also at risk of complications.

Etiopathogenesis

Influenza virus (Fig. 18.16), an RNA virus, has three strains:

1. Strain A is responsible for most of the human disease
2. Strain B causes only a mild illness
3. Strain C remains restricted to birds.

A remarkable feature of influenza antigen is its ability to undergo frequent mutation and reassortment (*drift* means minor change and *shift* means major change). As a result new viruses are born. To these new viruses, the population may have no immunity. Hence, outbreaks of illness occur annually (seasonal malaria). When there is a major change, i.e. shift, a large-scale epidemic crossing continental boundaries occurs (pandemic). This happens once in a while—on an average only thrice in a century or every 30–40 years.

Transmission and Spread

It is by airborne droplet or by direct contact. Having got entry into the airway, the virus attaches itself to the epithelium via the antigen, hemagglutinin and proliferates.

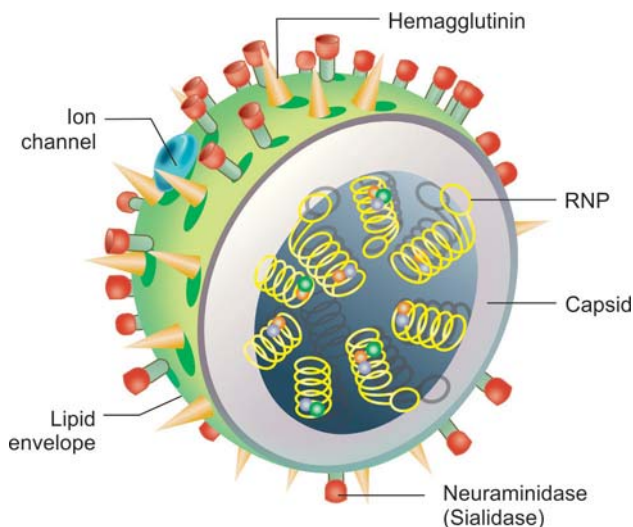


Fig. 18.16: Influenza virus: Note the structure—hemagglutinin and neuraminidase.

Abbreviation: RNP, ribonucleoprotein.

Table 18.2: Complications along with their clinical indicators of influenza

Complication	Clinical indicators
LRTI, pneumonia, bronchiolitis and bronchitis	Reappearance of high fever after temperature settling at normal, dyspnea
ARDS/respiratory failure	
Myocarditis	Tachycardia
Encephalitis	Seizures
GBS	Symmetrical ascending weakness/paralysis

Abbreviations: LRTI, lower respiratory tract infection; ARDS, acute respiratory distress syndrome; GBS, Guillain-Barré syndrome.

Clinical Features

Incubation period is short—just 1–3 days. Manifestation includes fever, bodily pains (especially headache), URI (rhinorrhea, sore throat, cough), diarrhea and vomiting.

Complications

In susceptible subjects (as already identified), in 4–5 days, one or the other complication may set in (Table 18.2).

Diagnosis

Diagnosis is based on high index of suspicion. Differentiation from common cold is important. Molecular diagnosis (PCR) and virus isolation, though available, has limited value.

Treatment

- In healthy subject with mild disease, treatment is symptomatic, comprising of antipyretics/analgesics, maintenance of fluid and nutrition and followed up for response and any complication.
- In high-risk subjects (with underlying risk factors), it is advisable to start currently recommended antiviral

drug, oseltamivir, 4–6 mg/kg/day in 2 divided doses for 5 days. Twice the normal dose may be given in the event of very severe illness. The other drug, zanamivir, may be employed in case of poor response to oseltamivir in severe cases or cases with underlying risk factors. M2 inhibitors (amantadine, rimantadine) are no longer recommended in view of high level of drug resistance.

Indications for additional antibiotic therapy such as amoxicillin, co-amoxiclav, cephalosporins, are suspected superadded bacterial infection (say bacterial pneumonia).

Prophylaxis

Conservative measures include, hand hygiene, cough etiquettes, use of appropriate surgical masks, etc. **Drug prophylaxis** consists of administration of oseltamivir daily for 10 days in very high-risk contacts of an influenza patient. **Influenza vaccine** is the most useful preventive measure. Every year a new influenza vaccine is developed based on likely strains.

- Two types of vaccines are used: Inactivated and live attenuated.
- Minimum age for vaccination is 6 months.
- Until 8–9 years, two doses are required, thereafter only one.
- Upto 2 years only inactivated vaccine (injectable) is permitted.
- After 2 years either inactivated or live attenuated vaccine may be used.

Research is in progress for developing a **universal vaccine** so that, with changing strains, there is no need to develop new vaccine every year. For details, See Chapter 10 (Immunization).

BIRD (AVIAN) FLU

Bird flu (avian influenza) is a contagious disease caused by certain viruses, usually in domestic poultry birds (chickens, ducks) and less frequently in pigs. The highly pathogenic viral strain, H5N1, is capable of jumping the species barrier (antigenic shift) and cause severe disease in humans with high mortality. What is worse, the avian virus is capable of crossreacting with the human influenza virus, leading to genesis of a new virus which may cause severe influenza epidemics in humans. Human to human spread, though rare, is possible. Antiviral drugs effective against the human infection are:

- **M2 inhibitors:** Amantadine, rimantadine (currently out of favor in view of development of resistance).
 - **Neuraminidase inhibitors:** Oseltamivir, zanamivir.
- Prophylaxis comprises of destruction of infected birds/animals, avoidance of handling of infected birds, full cooking of the chicken and quarantine of the infected individuals.

VIRAL HEPATITIS

On the basis of viral, immunologic and epidemiologic studies, at least 5 forms of viral hepatitis stand well recognized, namely hepatitis A, hepatitis B, hepatitis C, hepatitis D and hepatitis E. Hepatitis A, C, D and E are RNA virus whereas hepatitis B is a DNA virus. In addition, hepatitis F and G are

in the process of exploration and there are several nonhepatotropic viruses like CMV, EBV, herpes simplex virus (HSV), varicella zoster, HIV, mumps, adenovirus and echovirus that involve the liver. For details, See Chapter 30 (Pediatric Hepatology and Pancreatology).

SLOW VIRUS INFECTION

Certain viruses remain dormant over years but may flare up later at periods of debility and vulnerability. The very long incubation period and a slow course, terminating fatally, have earned them the name **slow virus infections or disease**. The other characteristics include:

- The course marked by remissions and exacerbations
- Predilection for CNS
- Absence or abnormal immune response
- A genetic predisposition.

Three groups of diseases are recognized:

1. **Group A:** Vinsa-Maedi, demyelinating disease and progressive hemorrhagic pneumonia respectively, caused by closely-related leukoviruses in sheep.
2. **Group B:** Subacute spongiform viral encephalopathy and Creutzfeldt-Jakob disease.
3. **Group C:** SSPE which is a delayed sequel to measles virus or live measles vaccine, and progressive multifocal leukoencephalopathy which occurs in elderly persons with impaired immune response due to malignancy or immunosuppressive therapy.

Recently, it has been suggested that slow virus infection may be classified as:

- Those caused by conventional viruses (refers to viruses with conventional physical properties and with manifestations of acute self-limited illness).
- Those caused by unconventional viruses (are agents that have physical properties very much different from conventional viruses but that are much smaller than bacteria). Table 18.3 lists the slow virus diseases falling under conventional and unconventional groups.

It is possible that slow virus infections are responsible for many more degenerative and other disorders. As for

Table 18.3: Two groups of slow virus infections

Conventional
<ul style="list-style-type: none"> • Subacute sclerosing panencephalitis • Progressive rubella panencephalitis • AIDS encephalopathy • Rabies • Cytomegalovirus encephalitis • Kozhevnikov's epilepsy • Tropical spastic paraparesis/HTLV-I-associated myelopathy • Progressive multifocal leukoencephalitis • Rasmussen chronic encephalitis.
Unconventional
<ul style="list-style-type: none"> • Kuru • Creutzfeldt-Jakob disease • Gerstmann-Straussler syndrome.

Abbreviations: AIDS, acquired immunodeficiency syndrome; HTLV, human T-lymphotropic virus.

instance, slow ECHO virus has been incriminated in the etiology of GBS.

EMERGING VIRUS INFECTIONS

The term emerging virus denotes:

- A newly discovered virus
 - One that existed long back, but was dormant
 - One that is increasing in incidence, or
 - One with the potential to increase in incidence.
- A number of viruses fall under the category of viruses.

The following five emerging viruses need special consideration:

1. Ebola virus
2. Chandipura virus
3. Nipah virus
4. Hanta viruses
5. Crimean-Congo hemorrhagic fever virus.

The salient features of these emerging virus diseases are listed in Table 18.4.

SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

See Chapter 26 (Pediatric Pulmonology).

Table 18.4: Emerging viral infections

Feature	Ebola virus	Chandipura virus	Nipah virus	Hanta viruses	Crimean-Congo hemorrhagic fever virus
About virus	<ul style="list-style-type: none"> • Family: Filoviridae, • Genus: Ebola virus. • The first Ebola virus species was discovered in 1976 in Congo near the Ebola River and Sudan. Since then, outbreaks have appeared sporadically. The 2014 outbreak in Western Africa appeared to be the worst. 	A ribovirus; So far seen in India only	Its hosts are fruit bats who transmit disease to man and pigs	Negative sense RNA viruses	<ul style="list-style-type: none"> • RNA virus, • Bunyaviridae family, • Usually infecting cattle but can infrequently infects man.
Transmission	<ul style="list-style-type: none"> • Spread from person to person, from the body fluids of infected individuals. • Risk of contracting Ebola is very low unless one visits an area where it is widespread. 	Infected Sandfly bite	Fruit bats	<ul style="list-style-type: none"> • Natural hosts are rodents. • Man acquires infection by inhalation of aerosols contaminated rodent excreta or saliva. 	<ul style="list-style-type: none"> • Infrequent transmission to man. • Human to human transmission occurs, very contagious. • In India, reported from Gujarat.

contd...

Feature	Ebola virus	Chandipura virus	Nipah virus	Hanta viruses	Crimean-Congo hemorrhagic fever virus
Disease	Ebola virus disease	Viral encephalitis	Viral encephalitis	<ul style="list-style-type: none"> Hemorrhagic fever with renal syndrome (Asia and Europe) Cardiopulmonary syndrome (America) 	Hemorrhagic viral fever
Clinical features	<ul style="list-style-type: none"> Manifestations usually begin suddenly with an influenza-like stage characterized by fatigue, fever, headaches, joint, muscle and abdominal pain, vomiting, diarrhea and anorexia. Ranging from mild to severe, Ebola affects many of the body's organs, causing bleeding and other symptoms, including death. Manifestations in children and adolescents are on same lines as in adults. 	Viral encephalitis with high mortality and morbidity in survivors in the form of neurological sequelae.	Fever followed by features of encephalitis; may cause LRTI with respiratory distress.	<ul style="list-style-type: none"> Febrile illness, body pains, headache, bleeding, renal failure; Leucocytosis with shift to the left. Thrombocytopenia, raised liver enzymes 	<ul style="list-style-type: none"> Dengue-like presentation; fever, bodily pains, headache, bleeding (extensive). Leucopenia, thrombocytopenia, deranged coagulation cascade, liver dysfunction, renal impairment and even failure, rhabdomyolysis.
Diagnosis	<ul style="list-style-type: none"> Depends on stage of disease: Within a few days after symptoms begin: Antigen-capture ELISA testing IgM ELISA PCR Virus isolation: Later in disease course or after recovery: IgM and IgG antibodies Retrospectively in deceased patients: Immunohistochemistry testing PCR Virus isolation 	By and large clinical	Clinical	Specific IgM antibodies	Specific PCR
Treatment	No effective treatment, except for supportive care	Only symptomatic and supportive	Symptomatic	Symptomatic, Ribavirin	<ul style="list-style-type: none"> Early administration of ribavirin Supportive measures Isolation
Prevention	Avoidance of contact with infected animals and persons	Avoidance of sandfly bite	Avoiding human exposure to raw date/palm juice contaminated by fruit bat excreta and infected pigs.		

Abbreviations: RNA, ribonucleic acid; LRTI, lower respiratory tract infection; PCR, polymerase chain reaction; ELISA, enzyme linked immunosorbent assay.

Multiple Choice Questions

- Spot the wrong observation about Koplik spots:
 - Sand-like minute lesions seen on the buccal mucosa
 - By the time rash appears, they virtually disappear
 - First seen opposite first upper molars
 - Have no bearing on the severity of illness
- Spot the wrong observation about pediatric HIV/AIDS:
 - A vast majority of cases result from parent-to-child transmission
 - Pneumonitis is often present
 - Lymphadenopathy is a common presenting feature
 - Kaposi sarcoma is common

contd...

3. Patent ductus arteriosus is a frequent accompaniment of:
 - A. Congenital rubella
 - B. Chickenpox
 - C. Roseola infantum
 - D. Mumps
4. Most frequent complication of mumps in a preschool child is:
 - A. Epididymo-orchitis
 - B. Pancreatitis
 - C. Aseptic meningitis
 - D. Pneumonia
5. Most frequent acute complication of measles is:
 - A. Pneumonia
 - B. Encephalitis
 - C. Diarrhea
 - D. Malnutrition
6. Typical skin lesion in chickenpox is:
 - A. Macular rash
 - B. Maculopapular rash
 - C. Vesicular rash
 - D. Pleomorphic rash

Answers

1. C 2. D 3. A 4. C 5. A 6. D

Clinical Problem-solving

Review 1

An 8-year-old who had suffered from poliomyelitis at the age of 1 year is by and large doing well, including academic performance as a class 3 student. Yet, his major handicap in the form of easy fatigability and foot drop is becoming a roadblock to some extent in his progress.

1. What could be the solution?
2. What are its main features?
3. Is it true that the child may develop new muscle weakness many years after?

Review 2

A 5-year-old girl, a known case of ventricular septal defect, suffering from coryza, sore throat and bodily pains is diagnosed as having “flu” on the basis of a rapid diagnostic test. She was put on symptomatic and supportive therapy. However, on third day of illness she develops severe cough, breathlessness and exacerbation of fever. CXR shows interstitial pneumonia which, the radiologist considers viral and “part of influenza illness”.

1. Is there any omission in initial treatment that may have invited such a complication as viral pneumonia?
2. What should be dose of the anti-influenza drug?
3. Any option, if this drug does not work?

Answers**Review 1**

1. The child should benefit from orthosis.
2. An **orthosis** is a device that externally supports an existing body part. In fact, besides supporting, it assists in correcting and compensating for skeletal deformity or weakness.
For the child under review, the thermoplastic leaf spring ankle foot orthosis, or drop foot splint, should be most appropriate. It assists dorsiflexion and uses 3 point pressure to stabilize the ankle joint.
3. Yes, post-polio syndrome may develop in 25–60% of polio patients, 30–40 years after the occurrence of the acute illness. It is characterized by new neurologic, musculoskeletal and general manifestations.

Review 2

1. Symptomatic treatment of flu is good enough in healthy subjects but not in subjects with underlying high-risk factors. This child, being a known case of ventricular septal defect, is a fit case for treatment with antiviral drug oseltamivir. Such a therapy usually succeeds in preventing complications, including viral pneumonia.
2. Routine pediatric dose of oseltamivir is 4–6 mg/kg/day in 2 divided doses for 5 days. In view of very severe illness in this child, twice the normal dose may be considered.
3. Zanamivir is a good option in case of poor response to oseltamivir.

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STAPHYLOCOCCAL INFECTIONS

Staphylococcus is a common cause of community-acquired as well as nosocomial infectious diseases in pediatric practice.

Microbiological Aspect

Staphylococcal group of Gram-positive cocci are of three types:

1. ***Staphylococcus aureus* (coagulase positive {Fig. 19.1})**: A normal flora of mucus membrane (nose, throat and rectum) and skin (axilla, perineum and vagina) of one-fourth of the healthy children.
2. ***Staphylococcal epidermidis* (coagulase negative)**: A normal flora of skin and mucus membrane.
3. ***Staphylococcal saprophyticus* (coagulase negative)**.

Epidemiology

Infection is spread by direct contact, through a carrier or via contaminated objects; occasionally it may be an air-borne transmission.

Pathogenesis

Though *Staphylococcus* is a normal resident in human host, it is likely to become pathogenic:

- In the presence of an immunocompromised state.
- In case of a breach in the mucocutaneous barrier.
- In case of a previous exanthemata such as measles and chickenpox.
- In the presence of implanted foreign prosthetic material such as a central venous catheter, or a shunt.
- Hospitalization when methicillin-resistant staphylococcus aureus (MRSA) and methicillin-resistant coagulase negative staphylococcus aureus (CONS) cause nosocomial infections.



Fig. 19.1: *Staphylococcus aureus*.

Clinical Features

Box 19.1 lists the superficial and deep infections caused by *staphylococci*.

Treatment

In view of increasing resistance to conventional penicillin and its derivatives, recommended antibiotics at present are

Box 19.1 Infections caused by *Staphylococcus*

Superficial staphylococcus infections (skin and soft tissues)

- Boils
- Furuncles
- Carbuncles
- Impetigo
- Paronychia
- Stye
- Superadded infection over atopic dermatitis
- Cellulitis (Fig. 19.2)
- Necrotizing fasciitis
- Lymphadenitis
- Abscess.

Deep staphylococcus infections

- Sepsis
- Respiratory infections—AOM, sinusitis, pneumonia, lung abscess, empyema
- Arthritis
- Osteomyelitis
- Pyomyositis
- Infective endocarditis
- Pyopericardium.

SSSS

- Exfoliation of superficial skin (stratum granulosum) along with bullae, fever and malaise, usually in neonates, but also in infants and children.
- Nikolsky sign* is positive, i.e. gentle touch causes separation of the areas of superficial epidermis leaving behind denuded areas of skin.

Staphylococcal food poisoning

Usually occurring within 6 hours following ingestion of contaminated foodstuff with symptoms such as fever, nausea, profuse vomiting, abdominal discomfort and, at times, diarrhea.

Disseminated staphylococcal disease

It is characterized by suppurative Staphylococcal infections involving several sites and a prolonged course.

Toxic shock syndrome

- A febrile illness that suddenly progresses to shock and multiorgan failure following fever, erythematous rash, gastrointestinal upset, myalgia, oliguria and change in sensorium.
- DIC.

Abbreviations: AOM, acute otitis media; SSSS, staphylococcal scalded skin syndrome; DIC, disseminated intravascular coagulation.

* After Pyotr Nikolsky (1858–1940), a Ukraine physician. In addition to staphylococcal scalded skin syndrome, it is positive in pemphigus vulgaris and toxic epidermal necrolysis (TEN) as well.



Fig. 19.2: Staphylococcal cellulitis. Note the widespread involvement of both superficial and deeper layers of skin.

penicillinase-resistant penicillin like cloxacillin, methicillin, cephalosporins and amoxiclav, provided the pathogens are methicillin-sensitive *Staphylococcal aureus* (MSSA).

For MRSA, recommended agents are vancomycin, linezolid and teicoplanin. Additionally, surgical drainage and removal of prosthetic material may also be needed.

HEMOPHILUS INFLUENZAE INFECTIONS

Microbiological Aspects

Hemophilus influenzae is a Gram-negative pleomorphic coccobacillus normally present in the nasopharynx in unimmunized subjects. Typable *H. influenzae* are of six serotypes, types a to f (Fig. 19.3).

Epidemiology

- **The most virulent strain:** *Hemophilus influenzae* type b (Hib); responsible for disease in 95% of the cases
- **Age group:** Around 90% of the cases are aged less than 5 years, the vast majority belonging to infancy
- **Mode of transmission:** Direct contact or a droplet infection. Humans are the only natural host
- **Incubation period:** Variable
- **Communicability:** Not defined
- **Predisposing factors include:**
 - **Population/ethnic groups:** Blacks, Eskimos, Apaches and Navajos
 - **Diseases:** Sickle-cell disease, asplenia, immunodeficiency states (both congenital and acquired) and malignancy
 - Previous history of a documented Hib disease.

Etiopathogenesis

Hemophilus influenzae type b causes invasive disease by entry into the intravascular compartment. Nontypable organisms cause problems by spread from nasopharynx to middle ear, sinuses and conjunctiva in newborns, infants and children.

Clinical Features

- **Common:** Meningitis, sepsis, epiglottitis, pneumonia, cellulitis, suppurative arthritis and pericarditis.

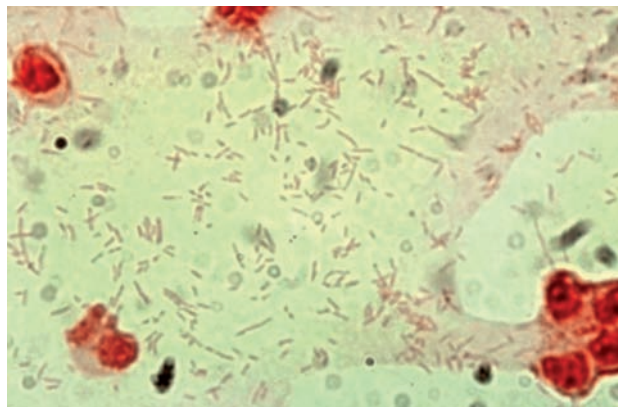


Fig. 19.3: *Hemophilus influenzae* type B.

- **Less common:** Invasive neonatal disease (sepsis, pneumonia, respiratory distress with shock, conjunctivitis, cellulitis and meningitis), otitis media and sinusitis.
- **Rare:** Urinary tract infection (UTI), cervical adenitis, epididymo-orchitis, glossitis, osteomyelitis, peritonitis, endocarditis and endophthalmitis.

Diagnosis

It is by:

- Identification of *H. influenzae* in smears or by culture.
- Serotyping employing slide agglutination with type-specific antisera.

Treatment

Initially, parenterally administered extended spectrum cephalosporins such as cefotaxime, ceftriaxone and cefixime should be employed because of their efficacy against ampicillin-resistant strains. Alternatively, chloramphenicol, ampicillin or amoxiclav (amoxycillin-clavulanate combination) may be given.

Later, an appropriate antimicrobial is selected depending on the culture sensitivity report; ampicillin being the drug of choice in susceptible isolates. Therapy can be completed with oral antibiotics like amoxiclav, cefixime or cefpodoxime. Chloramphenicol is an economical and effective option if strains are susceptible to it. Recommended duration for pneumonia/cellulitis is 7–10 days, for meningitis 10–14 days and osteomyelitis/arthritis 3 weeks.

Prevention

Hemophilus influenzae type b conjugate vaccine See Chapter 10 (Immunization) plays a remarkable role in drastically reducing incidence of Hib disease. It is available as monovalent or as a component of pentavalent (diphtheria tetanus and pertussis {DTwP}, Hib and hepatitis B {Hep B}) and hexavalent (diphtheria tetanus (acellular) pertussis {DTaP}, Hib, Hep B and injectable polio vaccine {IPV}) vaccines.

Chemoprophylaxis consists of administration of rifampicin, 10 mg/kg (O) below 1 month of age and 20 mg/kg (O) beyond this age, daily for 4 consecutive days, for the contacts as well as the index case.

STREPTOCOCCAL INFECTIONS

Of all the pathogens, *streptococci* are responsible for the most bacterial infections in childhood.

Microbiological Aspects

These are Gram-positive cocci arranged in shape of chains.

- Group A *streptococci* cause pharyngitis, tonsillitis and scarlet fever.
- Group B *streptococci* cause rheumatic fever through rheumatogenic strains and acute glomerulonephritis through nephritogenic strains.
- *Streptococcus viridans* cause infective endocarditis.
- *Streptococcus pneumoniae* (*Pneumococcus*) cause a wide variety of infections varying from noninvasive otitis media to invasive pneumonia, meningitis or sepsis.

PNEUMOCOCCAL INFECTIONS

Microbiological Aspects

Streptococcus pneumonia (*pneumococcus*) is a Gram-positive capsulated bacterium with 99 serotypes (Fig. 19.4). There is variation in the serotypes causing pneumonia from region to region. Most pneumonias in India are caused by serotype 7 unlike in USA where serotype 6 is dominant.

Epidemiology

The infection spreads from person to person through contact or droplets. High-risk groups include those with:

- Nephrotic syndrome
- Sick-cell disease
- Asplenemia (both functional and anatomical)
- Varicella
- Immunodeficiency
- Malignancy
- Cytotoxic drug administration.

Clinical Features

- Noninvasive
 - Upper respiratory tract infection (URTI)

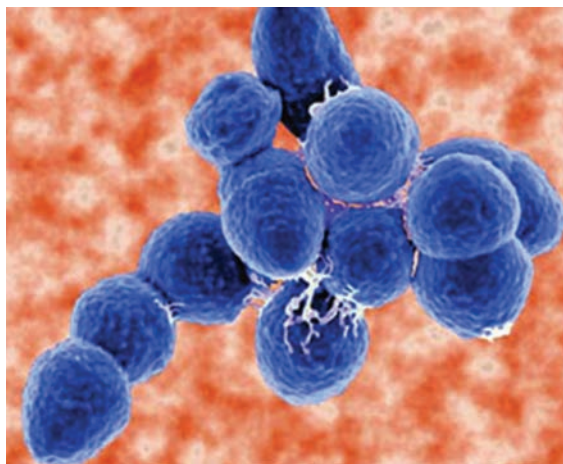


Fig. 19.4: *Pneumococcus*. This pathogen is the most common cause of pneumonia.

- Otitis media
- Mastoiditis
- Conjunctivitis
- Periorbital cellulitis
- Pneumonia—consolidation (lobar pneumonia)
- Bacteremia
- Toxic shock syndrome*.
- Invasive
 - Sepsis
 - Meningitis
 - Arthritis
 - Osteomyelitis
 - Infective endocarditis.

Diagnosis

It is mostly clinical. Investigations include:

- Complete blood count (CBC)
- Demonstration of pathogens on smear/culture.

Treatment

In view of widespread resistance to the conventional penicillin, currently drugs of choice are:

- Pathogens with intermediate resistance:
 - Amoxiclav and even penicillin in high doses may overcome intermediate resistance.
 - Cephalosporins (ceftriaxone and cefuroxime)
 - Macrolides (erythromycin, azithromycin and clarithromycin)
- Pathogens with high resistance:
 - Vancomycin
 - Quinolones.

MENINGOCOCCAL INFECTIONS

Ever since 1984, there have been outbreaks of meningococemia in Delhi, Uttar Pradesh, Rajasthan, Haryana, Jammu and Kashmir, West Bengal, Sikkim and Gujarat. Moreover, the predominance of the cases is during January through May. The disease is seen over twice as often in males as in females.

Etiology

The Gram-negative cocci, *Neisseria meningitides* (Fig. 19.5) a commensal in the nasopharynx of healthy individuals, may lead to disease, meningococemia, when the organisms invade the blood stream and disseminate to various parts. Various serotypes identified are types A, B, C, D, X, Y, Z, 29E and W135. Serogroup A is responsible for the disease in India.

Pathogenesis

The cell wall of the organism contains lipopolysaccharide, an endotoxin responsible for serious manifestations such as systemic toxemia, peripheral circulatory failure and disseminated intravascular coagulation (DIC). Bleeding into the adrenals occurs in subjects with septicemia and shock (**Waterhouse-Friderichsen syndrome**).

*Toxic shock syndrome (TSS) can follow both staphylococcal and streptococcal infections. Streptococcal TSS is less frequent, but more serious.

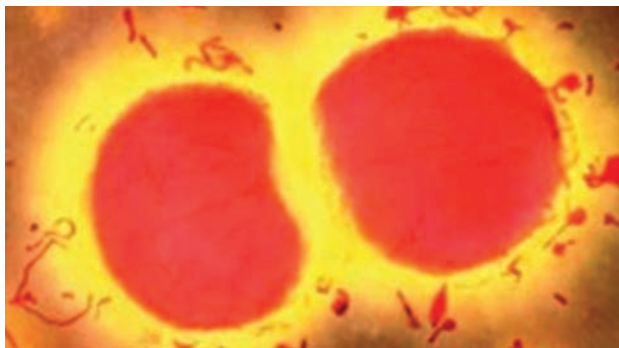


Fig. 19.5: *Neisseria meningitidis*.

Nasopharynx is the primary focus of infection, person to person spread occurring through respiratory droplet infection or close oral contact. Hematogenous spread occurs when the cocci penetrate the mucosa and are disseminated by leukocytes to blood stream. Factors that render a host susceptible to meningococemia include:

- Deficiency of terminal components (C5 through C9) of the complement system.
- Existing complement-depleting disease.
- Inherited deficiency of an alternative complement pathway component, properdin.
- Presence of B27 histocompatibility leukocyte antigen complex, deficiency of IgG₂ subclass, and sickle-cell disease.

Factors that heighten susceptibility of the host to systemic spread include extremes of climate and damage to nasopharyngeal mucosa by a viral infection such as influenza.

Clinical Features

Incubation period is 2–10 days. Various modes of presentation of meningococcal infection are:

- Upper respiratory infection with or without bacteremia is a self-limited common cold-like illness that resolves within a few days. Only in a small proportion of cases maculopapular rash may occur. Occasionally, conjunctivitis, cervicitis or urethritis may occur. This is also called *surface disease*.
- Acute meningococemia manifests as influenza like illness with fever, malaise, myalgia, headache and gastrointestinal tract (GIT) upset followed by a rash (morbilliform, petechial or purpuric)—the hallmark of the disease—hypotension, DIC, oliguria with progressive renal failure and coma. Most often the course is nonfulminant, but it may be fulminant with extensive purpura, hematogenous dissemination and shock which may not respond to treatment (Fig. 19.6).

Meningococcal meningitis results from hematogenous spread to meninges and is characterized by manifestations of meningeal irritation such as progressive drowsiness, vomiting, neck stiffness, and convulsions. Unlike very high incidence of meningitis in adult meningococcal infection, only one-half of the children suffer from this complication.

Acute endocarditis, myocarditis, pericarditis and pneumonia may be associated with meningococemia. Vulvo-



Fig. 19.6: Meningococemia. Note the extensive petechial, purpuric and ecchymotic spots.

vaginitis, urethritis, pelvic inflammation and endophthalmitis are rare complications.

Chronic meningococemia is characterized by anorexia, weight loss, pyrexia with chills, rash arthritis/arthralgia, erythema nodosum and endocarditis. It is rare in children and has periods of exacerbations and remissions, the course lasting for weeks to months.

Diagnosis

High index of suspicion goes a long way in identifying cases of meningococcal infection.

- Culture from nasopharynx leading to isolation of meningococci provides presumptive evidence of infection.
- Petechial skin lesions may be lanced (punctured) and smeared to see Gram-negative diplococci after Giemsa or Gram stain.
- **Blood:** Smear and culture.
- **Cerebrospinal fluid (CSF):** This investigation is a must in all cases suspected of meningitis. Biochemistry and morphologic picture is that of any pyogenic meningitis. Gram staining and culture may be positive.
- Rapid diagnostic tests include countercurrent immunoelectrophoresis, latex agglutination, radioimmunoassay on blood, CSF and urine, limulus lysate assay and Quellung reaction.

Treatment

The drug of choice is penicillin G, 3 lacs units/kg/day, administered intravenously (IV) in six divided doses. If exact etiology is not established, ampicillin may be given IV in a dose of 300 mg/kg/day in six divided doses. In case of penicillin allergy, chloramphenicol, 100 mg/kg/day, IV in four divided doses, cefotaxime, 200 mg/kg/day in 6 hourly doses IV or ceftriaxone 100–150 mg/kg/day, IV, may be employed.

Therapy must be continued for at least 7–10 days and until the patient is afebrile for at least 3 days in case of simple meningococemia and 5 days in case of meningitis.

For endotoxemic shock, dopamine (initial dose 2–5 µg/kg/min; then increased till blood pressure and urine output are satisfactory to as much as 20 µg/kg/min {if the need be}) and/or steroids (hydrocortisone or dexamethasone) are indicated. For DIC, fresh whole blood, fresh plasma or platelets as such or together with heparinization may be helpful.

Table 19.1: Chemoprophylaxis in meningococcal infections

Drugs	Doses	Duration/no. of doses
Rifampicin (Drug of choice)	10 mg/kg (O) (maximum of 600 mg) 12 hourly	48 hours (4 doses over 2 days)
Ceftriaxone	125 mg IM (single dose, once only)	1 dose
Ciprofloxacin	500 mg (O) single dose once only	1 dose

Prognosis

Overall mortality from meningococcal disease varies from 3% to 20%, the lower figure being for meningitis. Poor prognostic signs are:

- Hypotension
- Absence of meningitis
- Coma
- Rapidly progressive purpura, especially of less than 24 hours duration
- Hyperpyrexia
- Cardiac or renal failure
- DIC
- Leukopenia, thrombocytopenia, low erythrocyte sedimentation rate (ESR) and high serum antigen concentration
- Low CSF polymorphonuclear leukocyte count
- Long-term sequelae include sensorineural deafness and psychomotor disability.

Prevention

Chemoprophylaxis

This is indicated in household and day-care nursery contacts of an index case as per Table 19.1.

Vaccination

Indian meningococcal infections are caused by group A strains for which an effective vaccine is available. It is recommended for household and day-care nursery contacts of an index case as an adjunct to chemoprophylaxis. A single dose is effective, taking about 2 weeks to act. Booster doses after 3 months and 12–18 months are said to provide additional protection. Use of meningococcal vaccine for normal children as a part of routine vaccination is not recommended. Also, See Chapter 10 (Immunization).

DIPHTHERIA

Diphtheria (Greek term meaning a membrane) is an acute bacterial disease, characterized by formation of a membrane, primarily in the upper respiratory tract, and toxemic manifestations as a result of liberation of a powerful *exotoxin*.

It is rare under 6 months of age. Preschoolers are very prone to it. However, the age incidence is now rising. Today, diphtheria is often seen in adolescents and adults as well. This is perhaps due to increased level of vaccination early in life with poor coverage in later years.

Etiopathogenesis

It is caused by *Corynebacterium diphtheriae*, a Gram-positive pleomorphic rod that grows on Loeffler medium.

Epidemiology

Diphtheria occurs all over the world. It is in the winter months that maximum incidence is reported. In the developed areas, it tends to attack the grown-up children, the adolescents and the adults. This again appears to be related to the increased immunization among the infants and children in these areas.

Transmission of infection is by droplets from an individual with active disease or a carrier. A powerful necrotizing exotoxin that gets fixed to the tissues is responsible for signs and symptoms. The manifestations depend on the site of the membrane and its extent as well as on the age of the patient rather than the strain of the organism.

Clinical Features

Diphtheria has a short incubation period, i.e. 3 days, the extremes being just 1 day and 6 days. Clinical picture depends on the location of membrane, its extent and the age of the subject. The following types are recognized:

Faucial Diphtheria

Tonsils are the most frequent site of diphtheria in pediatric practice. The manifestations are:

- Sore throat and difficulty in swallowing
- General malaise and prostration
- Tachycardia
- Moderate fever
- Membrane—the aforesaid manifestations are followed by formation of a whitish-gray membrane, firmly attached to the underlying mucosa over tonsils, anterior pillars and uvula (Fig. 19.7). It may extend over to the pharynx. It is difficult to remove the membrane without damaging the mucosa and thus without a bleed. The maneuver should, however, be avoided since it may cause greater liberation of the damaging toxin
- Cervical lymphadenopathy in severe cases.



Fig. 19.7: Faucial diphtheria: Note the grayish white membrane firmly adherent to the underlying tonsils and surrounding structures.

364 Laryngeal Diphtheria

Most serious but, fortunately, less common. The manifestations are:

- Hoarseness, aphonia and croup
- Brassy or barking cough
- Dyspnea and cyanosis in case of severe respiratory distress
- Restlessness and anxiety
- Prostration
- Bull-neck due to gross cervical lymphadenopathy and brawny edema of the neck
- Membrane—It is usually the extension of the membrane of the throat (faucial diphtheria) lower down into the larynx. Membrane may, however, be merely limited to larynx in a minority of the cases. The first is called **secondary laryngeal** and the second the **primary laryngeal** diphtheria. Membrane in the larynx can readily be seen on laryngoscopy.

Nasal Diphtheria

It is uncommon (only 1–3% of all the cases of diphtheria), but a potent source of spread of infection to others. It occurs in infants. The manifestations are:

- Visible membrane over turbinates
- Nasal discharge (serosanguinous and foul-smelling) which may be unilateral or bilateral
- Frank epistaxis may occur occasionally
- Excoriation of nose and upper lip
- Nasal obstruction
- Slight constitutional symptoms.

Cutaneous and other Rare Diphtheria

Diphtheric membrane may be found on skin, open wounds, genitalia and conjunctiva, and in ears. The underlying ulcers are often painless and chronic.

Diagnosis

Diagnosis is primarily clinical. In a suspected case, immediate action should be taken to examine the smears from throat swab (or other affected site). When stained with methylene blue, the organisms are seen as rods with mid-polar bar. Culture on Loeffler medium is of value. Results of culture are available within 8 hours. For quick diagnosis, fluorescent antibody technique is of greatest help.

Complications

Various complications of diphtheria are listed in Box 19.2.

Treatment

Specific treatment consists of immediate administration of antitoxin, i.e. anti-diphtheritic serum (ADS), 20–100 thousand units IM, IV or both. The actual dose would depend on the site and extent of membrane and degree of toxemia (Table 19.2). Needless to say, ADS should only be administered after the sensitivity test to guard against the risk of anaphylactic reaction. Desensitization is needed in case of sensitivity to ADS (Box 19.3).

Antibiotics (preferably procaine penicillin or erythromycin; alternatively amoxycillin, rifampicin or

Box 19.2 Various complications occurring in diphtheria

Serious

- **Myocarditis:** It may occur any time during the course of the disease. The early development is a bad prognostic sign.
- Vasomotor disturbances in the form of hypotension and cardiac failure 2–3 weeks after onset of the disease, occur rarely.
- **Paralysis:** About 12–21% of the cases suffer from the post-diphtheritic paralysis somewhere between first and sixth week of illness. The following are the various types seen:
 - Pharyngeal and palatal paralyses are manifested by nasal voice, dysphagia, nasal regurgitation, and failure to lift the palate
 - Ocular paralysis occurs late and is second in frequency. It is manifested in the form of diplopia, squint, ptosis, ophthalmoplegias, etc.
 - General paralysis occurs quite late. There may be quadriplegia, paralysis of the neck muscles and respiratory embarrassment, as a result of involvement of the diaphragm from phrenic nerve paralysis. Even CSF protein may be elevated. This complication closely simulates GBS.

Mild to Moderate

- Respiratory infection—bronchopneumonia
- Nephritis (mere albuminuria in early stages)
- Gastritis
- Hepatitis.

Abbreviations: CSF, cerebrospinal fluid; GBS, Guillain-Barré syndrome.

Table 19.2: Recommended dosage of anti-diphtheritic serum for treatment of diphtheria

Situations	Dosage range (units)
Anterior nares, laryngeal or pharyngeal diphtheria of 48 hours or less duration	20,000–40,000
Nasopharyngeal diphtheria	40,000–60,000
Extensive disease of over 3 days duration or with brawny neck edema	80,000–100,000

Box 19.3 Recommended regimen for desensitization in case of ADS

- 0.1 mL of 1:1,000 saline dilution (IV) followed by an increment every 15 minute if no anaphylaxis occurs
- 0.3 mL of 1:1,000 saline dilution (IV)
- 0.6 mL of 1:1,000 saline dilution (IV)
- 0.1 mL of 1:100 saline dilution (IV)
- 0.3 mL of 1:100 saline dilution (IV)
- 0.6 mL of 1:100 saline dilution (IV)
- 0.1 mL of 1:10 saline dilution (IV)
- 0.3 mL of 1:10 saline dilution (IV)
- 0.6 mL of 1:10 saline dilution (IV)
- 0.1 mL of undiluted ADS (IV)
- 0.2 mL of undiluted ADS (IV)
- 0.6 mL of undiluted ADS (IV)
- 1.0 mL of undiluted ADS (IV).

Abbreviations: ADS, anti-diphtheritic serum; IV intravenously.

clindamycin) should be administered for 2 weeks. The aim is to stop production of diphtheria toxin, eradicate the organisms, prevent their spread and eradicate group. A β -hemolytic streptococci that are known to complicate up to one-third patients of diphtheria. Only after three negative cultures, the patient is considered cured. Carrier state is effectively treated with penicillin G or erythromycin.

During convalescence, if **Schick test** is positive, diphtheria toxoid should be given since not all subjects develop adequate immunity after the disease. **General measures** include proper bed rest for about 2 weeks, isolation, maintenance of fluid and dietetic adequacy (may need tube feeding or IV fluids), antipyretics, frequent aspiration and high humidity. Tracheostomy and mechanical respirator may also be needed in case of respiratory obstruction or paralytic involvement of the diaphragm.

Prophylaxis

The only reliable method of achieving this is active immunization with DTP. See Chapter 10 (Immunization). All close contacts need to have Schick test and culture.

- If the contact is Schick positive as well as culture positive, full treatment for diphtheria must be instituted.
- If Schick test is negative but culture is positive, the contact should be considered a carrier.
- If the carrier is immunized earlier, he needs a booster dose of toxoid and erythromycin or benzathine penicillin.
- If he is not (that include subjects whose immunization status is not known), he should receive first dose of toxoid and 5,000–10,000 units of ADS (IM).

Prognosis

It is guarded. Almost 50% of the cases die if left untreated. With recommended treatment, mortality is around 4–5% and is usually the result of myocarditis. Institution of specific therapy on the very first day of disease may reduce the mortality to as low as less than 1%. Delay in instituting specific therapy until the fourth day raises the mortality about 20 times. The survivors do not, as a rule have any paralytic sequelae. Infrequently, diphtheria may cause permanent cardiac damage.

PERTUSSIS

(Whooping Cough)

Pertussis is a highly communicable bacterial infection characterized by catarrhal symptoms followed by bouts of cough which further worsen to **inspiratory whoop**. It is primarily a disease of preschoolers and may occur in a newborn even. Preschoolers are responsible for 50% of the total cases. A single attack confers lifelong immunity in a vast majority of the cases.

Etiopathogenesis

The causative organism is a nonmotile, rod-shaped Gram-negative bacillus, *Bordetella pertussis*, *Bordetella paraper-tussis*, *Bordetella bronchiseptica*. *Hemophilus hemolyticus* and adenovirus infection (types 1, 2, 3 and 5) may produce similar though mild disease.

Transmission is mostly by droplet infection and occasionally by contact with contaminated objects. Infectivity remains from 1 week prior to and 3 weeks after onset of typical paroxysm. Pathological involvement of the respiratory tract from nasopharynx to bronchioles, producing

Table 19.3: Major antigens and toxins responsible for pertussis pathology and symptom complex

Toxins	Mechanism of actions
Major antigens	
Filamentous hemagglutination	Attachment of the pathogens to the antigen (filamentous hemagglutinin) respiratory epithelium
Lymphocytosis promoting	Absolute LPF
Toxins	
ACT	Inhibits phagocytic function
DNT	Local epithelial damage
PT	Attachment of the pathogens to the respiratory epithelium; inhibits phagocytic function
TCT	Disrupts mucociliary clearance; damage to the epithelium

Abbreviations: LPF, lymphocytosis promoting factor; ACT, adenylate cyclase toxin; DNT, dermonecrotic toxin; PT, pertussis toxin; TCT, tracheal cytotoxin.

inflammatory reaction of the mucosa and secretions (phlegm) is responsible for most of the manifestations.

A number of antigens and toxins contribute to pathology and the resultant manifestations of pertussis (Table 19.3). Whereas most of these cause local pathology, pertussis toxin (PT) is primarily responsible for systemic manifestations.

Clinical Features

Whooping cough has an incubation period of 6–21 days with a mean of 7 days. Three stages, each of about 2-week duration, are known.

1. **Catarrhal stage:** Onset is usually insidious with catarrhal symptoms, i.e. rhinitis, sneezing, lacrimation, fever and irritating cough which is nocturnal to begin with, but later becomes diurnal.
2. **Paroxysmal (Spasmodic) stage:** Cough comes in paroxysms and is accompanied by vomiting. A typical attack consists of repeated series of many a cough-in-expiration followed by a sudden, deep, violent inspiration with characteristic crowing sound which has earned the designation whoop. It is due to laryngospasm. The patient appears suffocated with congested (red) face, with or without cyanosis, and anxious look (Fig. 19.8). Sweating, congestion of neck and scalp veins and confusion may follow the spells. Periorbital edema, subconjunctival hemorrhage, ulcer of frenulum of tongue, exhaustion, dehydration and convulsions may complicate the clinical picture. The paroxysm may be triggered by eating, yawning, sneezing, drinking, any other sudden movement, change in room temperature and even by a suggestion.
3. **Convalescent stage:** Here, disturbing cough and vomiting stop. Appetite too improves. The so-called **habit pattern** of coughing may, however, linger on over subsequent weeks and months. This has led the Chinese call it **cough of 100 days**. Lung complications such as atelectasis, bronchopneumonia or bronchiectasis are known to significantly prolong the convalescence.



Fig. 19.8: Pertussis. Note the facial appearance during a typical paroxysm. Such factors as eating, sudden movements and change in room temperature precipitate paroxysms.

Diagnosis

Clinical

It is easy to recognize a typical case, especially in the second stage. The disease should be differentiated from whoop produced as a result of pressure of enlarged paratracheal lymph nodes in tuberculosis and Hodgkin disease. It needs to be remembered that a pertussis-like syndrome may result from infection with *Bordetella parapertussis*, *Bordetella bronchiseptica*, *Hemophilus hemolyticus*, adenoviruses and foreign body in the airway. As has been rightly put—**everyone producing a whoop does not necessarily suffer from whooping cough.**

Investigative

- The white blood cell (WBC) count is initially low, but then rises far beyond the normal, varying from 20,000/mm³ to 50,000/mm³.
- There is, however, remarkably high absolute lymphocytosis, always above 50% and frequently as high as 90%. This feature is quite suggestive of whooping cough.
- The ESR is, however, extremely low. In fact the triad of whoop, lymphocytosis and low ESR strongly favors the diagnosis of pertussis.
- Chest X-ray may demonstrate perihilar infiltration, atelectasis or emphysema.
- The only definite means of arriving at the diagnosis is the positive nasopharyngeal culture on **Bordet-Gengou medium** or **Regan-Lowe medium**. This is warranted in the first stage and in the atypical cases. In place of nasopharyngeal swab technique, the cough-plate method can also be employed.
- For rapid diagnosis, fluorescent antibody test on the laryngeal swab, counter immunoelectrophoresis (CIE) and deoxyribonucleic acid (DNA) probe are of value.
- Enzyme linked immunosorbent assay (ELISA) may be employed to detect serum IgM, IgG and IgA to filamentous hemagglutinin and pertussis toxin.

Box 19.4 Various complications of pertussis

Respiratory

- Otitis media is quite frequent.
- Pneumonia (including interstitial pneumonia) is a very serious complication, especially in infants
- Collapse, emphysema, bronchiectasis, pneumothorax and pneumomediastinum; surgical emphysema.

Neurological

- Convulsions and even encephalitis due to cerebral anoxia.
- Hemiplegia and mental subnormality may be left as a sequelae. Causes of seizures in pertussis include cerebral hypoxia related to asphyxia, hyperpyrexia, hyponatremia resulting from syndrome of inappropriate anti-diuretic hormone (SIADH) and alkalosis secondary to loss of gastric contents resulting from persistent vomiting.

Hematological

- Epistaxis
- Subconjunctival hemorrhages
- Cerebral hemorrhage.

Violent cough strain

- Frenular ulcer
- Rupture of diaphragm
- Rectal prolapse and umbilical and inguinal hernia.

Miscellaneous

- Flaring up of a pre-existing dormant tuberculous focus.
- Malnutrition as a result of frequent vomiting and disinclination to eat.

- The most sensitive and specific test for acute infection is IgG directed toward pertussis toxin.

Complications

The incidence of complications in pertussis is high (Box 19.4).

Treatment

General Measures

These consist of isolation of the patient, sedation, cough sedatives, and liberal use of oxygen to reduce anoxia and brain damage in severe type of disease. Maintenance of fluid and dietary intake is important. Feeds should be small, but frequent. The child tolerates the small feed better after the paroxysm.

Pharmacotherapy

Erythromycin (preferably the estolate ester) is the antibiotic of choice. If given within 2 weeks of onset of disease, it is capable of aborting or eliminating pertussis. If started after the onset of paroxysmal phase, it still reduces communicability and safeguards against superimposed bacterial infections. Symptoms are, however, not significantly reduced. It should be administered in a dose of 50 mg/kg/day in 3–4 divided doses for 2 weeks. It acts by eliminating pertussis organisms from the nasopharynx within 3–4 days.

Roxithromycin, azithromycin or clarithromycin, for just 5–7 days, gives as good or even superior results to 2-week course of erythromycin. Alternatively, cotrimoxazole, ampicillin, amoxycillin or chloramphenicol may be employed. Betamethasone and salbutamol (preferably nebulization) may be employed in selected cases of severe coughing

paroxysms. Use of pertussis immunoglobulin in the first week of disease may considerably reduce the whoop but not cough and vomiting.

The treatment of complications will depend on their individual nature. Frenular ulcer shows speedy healing if touched with silver nitrate.

Prophylaxis

Active immunization with DTP (both DTwP and DTaP) is outlined in Chapter 10 (Immunization). Only whole cell vaccine for primary vaccination should be used unless there is a contraindication.

Close contacts, especially neonates of mothers with pertussis, must receive erythromycin estolate for 2 weeks. Those under 7 years and previously immunized need to receive a booster dose of DTP, unless a booster dose has been administered in the preceding 6 months, as well. The contacts who have not been immunized earlier should receive erythromycin for 2 weeks after the contact is broken, until cough in the index case ceases, or until the index case completes 7 days course of erythromycin. In institutionalized epidemics, monovalent pertussis vaccine together with erythromycin is recommended.

Prognosis

Pertussis carries a poor prognosis in infants below 1 year of age. There is high morbidity and mortality in the event of complications. Beyond 1 year of age, the prognosis is good provided serious complications have not occurred. Long-term sequelae of pertussis in infancy include minor abnormalities of lung function and wheezing and other lower airway manifestations in adulthood.

TETANUS

Tetanus is an acute bacterial disease, characterized by painful spasms and stiffness of muscles as a result of a powerful neurotoxin. Recurrences are rare. India stands declared neonatal and maternal tetanus-free in 2015.

Etiopathogenesis

The causative organism, *Clostridium tetani*, is widely distributed in the soil, dust and feces of animals and humans. Transmission is usually through invasion of an injury (however minute) with the tetanus bacilli or contaminated umbilical cord in the newborn (neonatal tetanus). The bacilli, after entering the circulation, get attached to the motor endplate in muscles and motor nuclei in the nervous system.

Clinical Features

Incubation period varies from 3 days–14 days. The minimum recorded is 1 day and the maximal several months. Shorter the incubation period, severe the disease. Three varieties of tetanus are usually recognized, namely localized, generalized and cephalic.

- **Localized tetanus** is characterized by pain, constant rigidity and muscle spasm in the region of the injury.



Fig. 19.9: Tetanus: Note the classical spasm.

- **Generalized tetanus** usually has a sudden onset with muscle spasm and cramps, particularly about the location of inoculation, back and abdomen. The earliest manifestation in a newborn may be the refusal to take feed which should arouse suspicion. Restlessness, irritability, difficulty in swallowing (even difficulty in sucking) and, at times, convulsions soon follow.

A typical tetanic spasm lasts for 5–10 seconds and consists of agonizing pain, stiffness of the body (Fig. 19.9) which gets almost arched backward with retraction of head (**opisthotonos**) and clenching of jaw and hands. As the disease progresses, a very simple stimulus also precipitates an attack. In advanced cases, spasms may become almost a continuous and constant feature.

- **Cephalic tetanus**, a rare variety of tetanus, is characterized by paresis or paralysis of one or more of the cranial nerves (usually 7th) in addition to the spastic manifestations which may initially be confined to head and neck but, usually later, involve rest of the entire body.

Diagnosis

In a large majority of cases, the clinical picture is sufficiently diagnostic. Tetanus bacilli may be cultured from excised necrotic tissue. This procedure is, however, hardly needed. Moreover, it is not feasible in areas where the disease is most endemic.

Complications

- **Resulting from respiratory muscle spasm:** Aspiration pneumonia, atelectasis, mediastinal emphysema and pneumothorax.
- **Resulting from tetanic seizures:** Laceration of tongue, buccal mucosa, etc. intramuscular hematomas and vertebral fractures.
- **Resulting from poor intake:** Malnutrition, dehydration and dyselectrolytemia.
- **Resulting from poor autonomic stability:** Myocarditis, arrhythmias, hypertension and hypotension.

Treatment

Anti-tetanus Serum (ATS)

The cornerstone of specific therapy is the **antitoxin**. ATS should be administered in a dose of 1,00,000 IU to children

368 and 30,000–50,000 IU to newborns immediately after making a clinical diagnosis.

Additional measures include simultaneous active immunization with toxoid, antibiotic (usually penicillin in high doses), human tetanus immunoglobulin (HTIG), sedation, control of spasms and supportive measures.

Prophylaxis

Active immunization is outlined in Chapter 10 (Immunization). Remember that active immunization of pregnant mother with tetanus toxoid is an effective and definitive preventive measure. Previously immunized mothers need just one dose and not 2 doses recommended for the non-immunized ones.

For **passive immunization**, ATS should be given in doses of 1–3 thousand IU, IM, the dose varying with child's age. At the same time, it is better to give 1 mL toxoid subcutaneously (SC). Two more injections of toxoid should be given later at 1 month intervals. This recommendation is for nonimmunized individuals with dirty and deep wounds. These patients should also have adequate surgical toilet of the wounds and injectable penicillin.

As for previously immunized subjects, a recall dose of toxoid suffices. Conduction of deliveries, both in and outside the hospital, under clean and aseptic conditions and application of clean dressing during healing of cord are also important.

Prognosis

A proportion of the survivors of neonatal tetanus may end up with cerebral palsy, paralysis, mental retardation, and behavioral problems as sequelae of apnea and anoxia resulting from prolonged attacks of spasms. A survivor from tetanus needs active immunization since tetanus does not confer immunity against future disease.

TYPHOID FEVER (Enteric Fever)

An acute bacterial infection, characterized by constitutional symptoms like prolonged pyrexia, prostration and involvement of spleen and lymph nodes. It does not cause lifelong or even sufficiently prolonged immunity. Second attack often occurs.

Etiopathogenesis

The disease is caused by *Salmonella** *typhi* and *Salmonella paratyphi* A, B and C** lead to a typhoid-like illness, the so-called **paratyphoid fever**. The typhoid and paratyphoid fevers are collectively known as **enteric fever**. In our country, at least 90% cases of enteric fever are due to *S. typhi*. This is perhaps true of most other tropical and subtropical regions, especially where standards of sanitation and hygiene are poor. Transmission is by contaminated food, unboiled milk, vegetables or water. Housefly plays a significant role

by carrying bacilli from urine or stools of an active sufferer or a carrier to food.

After ingestion, there is initial proliferation of the organisms in the lymphoid tissue of intestines (mostly in ileum), resulting in swelling of the **Peyer's patches**. This is followed by invasion of the blood stream. It is about this time that onset of clinical symptoms occurs. Toward the fag end of second week, ulceration of ileum results from shedding of intestinal lymphoid tissue. Additional pathologic changes include enlargement of mesenteric lymph nodes, focal necrosis of liver, splenomegaly, myocarditis, muscle degeneration and respiratory infection.

Epidemiology

Typhoid has a worldwide distribution. In the West, its incidence has declined to the point of near rarity. This is because of rising standards of sanitation and hygiene. In India and other developing countries, typhoid, however, continues to be a major public health problem. Poor sanitary conditions, lack of safe drinking water, illiteracy, ignorance, low standards of personal, group and community hygiene—all contribute to this unfortunate state of affairs.

The peak incidence of typhoid occurs in summer and rainy season when fly population shows enormous increase. Contrary to the popular belief and West-oriented teaching, typhoid is certainly common in infants and young children in countries of the Third World. A recent survey in a slum-population of Delhi revealed an overall incidence of 9.9 per 1,000 with an almost three-fold higher incidence in children under 5 years. No doubt, the clinical picture in pediatric typhoid is remarkably different from what is often seen in the grown-ups. Needless to say, chronic carriers happen to be the major source of spread of infection.

Clinical Features

Incubation period is 10–14 days with extremes of 5 and 40 days. Unlike adults, who show insidious onset with step-ladder rise in temperature, typhoid in children often manifests suddenly.

- The manifestations are rapid rise of temperature, extreme malaise, anorexia, headache, vomiting, and abdominal pain and distention. The paradoxical relationship of low pulse rate and high pyrexia is not common in children.
- **Some cloudiness of consciousness** (this is what the term, **typhoid**, denotes) is almost always present. Diarrhea is seen more often than constipation. Abdomen has a characteristic **doughy feel**. Spleen and, at times, liver are significantly palpable (Fig. 19.10). Bradycardia, an important sign in adults, is not a common finding in pediatric patients.
- A rash (macular red rose spot) is said to appear about the fifth day on the front and the back of the trunk. In

* Besides enteric fever, *Salmonella* may cause (1) septicemia, (2) enteritis/dysentery, (3) meningitis, (4) pneumonia/bronchitis, (5) osteomyelitis, (6) appendicitis and (7) peritonitis.

** *Salmonella paratyphi* C infection is very uncommon.

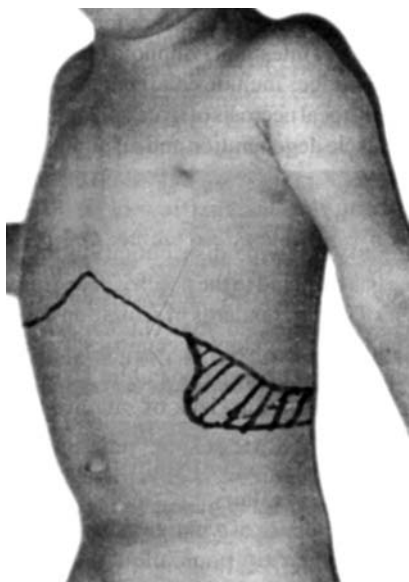


Fig. 19.10: Enteric fever. Note the splenomegaly detected in the third week. Widal test showed an “O” antibody titer of 1 in 240. The child had been admitted for unexplained fever of 18 days duration.

India, such a rash is, in actuality, very infrequently seen. This appears to be the result of two factors—(1) many cases of typhoid do not at all have it, and (2) most of our population is dark-skinned in whom it is difficult to see it.

- Sometimes, manifestations of typhoid may simulate the clinical picture seen in bacillary dysentery, respiratory infection or meningitis.
- In typhoid of infancy and early childhood, clinical profile usually includes fever with or without diarrhea, convulsions and, particularly, anemia. Anemia may be secondary to blood loss or hemolysis from auto antibodies.

Typhoid spares no age. Even neonates may develop the disease as a result of vertical transmission. **Neonatal typhoid** manifests, 72 hours after birth, with vomiting, abdominal distention, diarrhea and pyrexia of variable intensity. Accompanying manifestations include seizures, jaundice, hepatomegaly, anorexia and weight loss.

Differential Diagnosis

Tuberculosis, malaria, dengue, kala-azar, brucellosis, UTI and reticulosis are among the important differential diagnoses. Onset with acute abdomen and vomiting may suggest an abdominal emergency, like appendicitis, in which case an unnecessary surgery is likely to be resorted to. In the presence of chest manifestations, a typical bronchopneumonia may require to be excluded. If meningeal signs are there, meningitis must be ruled out.

Diagnosis

Clinical

The most important is the clinical suspicion. Any persistent pyrexia of unknown origin must be suspected of being typhoid fever and investigated accordingly.

Investigations

- Eosinopenia or complete absence of eosinophils is a reliable finding. Leukopenia with relative lymphocytosis, described as an important feature of typhoid, is most often absent. This is perhaps due to the fact that the patients generally report fairly late, particularly in developing countries.
- Blood and bone marrow culture for *S. typhi* is the most reliable method under ideal conditions. Positive cultures may be obtained at any stage of typhoid.
- **Widal test** is another important diagnostic tool. In our conditions of endemicity of typhoid, a ‘O’ antibody titer of 1 in 160 or more in the second week of symptoms is suggestive of the disease. A rising titer over a period of 7–10 days is, however, of greater value. In order to exclude the anamnestic responses, it is advisable to perform a modified Widal test along with a conventional Widal test. The chances of Widal test turning to be positive in the second week are around 60% and in the third week 80%.
- Rapid serodiagnostic procedures, especially CIE, ELISA and coagglutination (COAG) are now emerging as reasonably sensitive, specific, simple and economic diagnostic tools.
- In suspected chronic carriers, urine and stool cultures should be done. In strongly suspected cases with negative cultures of urine and stool, duodenal aspirate needs to be cultured.

Complications

Unlike adults, children with typhoid fever have far less incidence of abdominal complications. Extra-abdominal problems, especially those of respiratory and nervous system, are, however, more frequently encountered (Box 19.5).

Treatment

Specific

On account of emergence of multidrug-resistant strains (MDRS), conventional antityphoid agents such as chloramphenicol, amoxycillin, ampicillin, cotrimoxazole stand replaced by third generation cephalosporin like ceftriaxone,

Box 19.5

Various complications occurring in typhoid fever

- **Abdominal:** Intestinal perforation, hepatitis, liver abscess, fatty liver, cholecystitis and urinary tract infection.
- **Respiratory:** Bronchopneumonia, lobar pneumonia, bronchitis, pleurisy, empyema and pulmonary infarction.
- **Cardiovascular:** Toxic myocarditis, pericarditis, endocarditis, arteritis and venous thrombosis.
- **Neurologic:** Encephalopathy, meningitis, myelitis, Guillain-Barré syndrome, cranial nerve involvement, choreiform movements, monoplegia, hemiplegia, acute cerebellar ataxia, aphasia, psychiatric syndromes like acute confusion, severe depression and schizophrenia.
- **Hematologic:** Hemolytic anemia, bone marrow depression, consumptive coagulopathy and hemolytic uremic syndrome.
- **Miscellaneous:** Superficial abscesses and boils, bed sores, bleeding, parotitis, otitis media, tonsillitis, alopecia, etc.

Table 19.4: Antibiotic therapy in typhoid fever

Drugs	Dosage	Remarks/ADRs
Conventional agents		
Chloramphenicol	50–100 mg/kg/day (O) in 4 divided doses × 10–14 days	Once drug of choice; resistance observed in 1990s to it is now on decline on account of its restricted use
Cotrimoxazole	10 mg/kg/day (O) in term of trimethoprim 50 mg/kg/day in term of sulfamethoxazole in 2 divided doses	Resistant strains
Ampicillin	100–200 mg/kg/day in 4 divided doses	Resistant strains
Amoxycillin	100 mg/kg/day in 4 divided doses	
Furazolidone	8–10 mg/kg/day in 3–4 divided doses	Effective with equivocal results. Resistant strains
New agents		
Cefixime	20 mg/kg/day (O) in 2 divided doses × 2 weeks	May be employed as such or as a switch over therapy
Cefotaxime	100 mg/kg/day (IM, IV) × 10–14 days	
Ceftriaxone	100 mg/kg/day (IM, IV)	
Ciprofloxacin	20 mg/kg/day (O) in 2 divided doses	May be avoided in small children because of speculated risk of arthropathy from damage to the cartilage
Ofloxacin	10 mg/kg/day (O) in 2 divided doses	— Do —
Azithromycin	20 mg/kg/day (O) ODS × 10 days	A cumulative drug; best administered on empty stomach.

Abbreviations: ADRs, adverse drug reactions; IM, intramuscularly; IV, intravenously.

Table 19.5: Pharmacotherapy for uncomplicated and complicated cases

Types of typhoid	Recommended drugs
Uncomplicated typhoid	
• Fully sensitive	Chloramphenicol, amoxycillin
• Multidrug resistant	Cefixime, fluoroquinolones
• Quinolone resistant	Azithromycin, ceftriaxone
Severe/complicated typhoid	
• Fully sensitive	Ceftriaxone
• Multidrug resistant	Fluoroquinolones
• Quinolone resistant	Ceftriaxone

cefixime, cefoperazone, ceftibuten, etc. or quinolones (ciprofloxacin, ofloxacin) or azithromycin (Tables 19.4 and 19.5).

Oral cefixime has been found to be an effective switch or step-down therapy, i.e. switching from an IV therapy (say with ceftriaxone) after a few days (say 2–3 days) when the patient's condition has improved. Other agents which are good for switch therapy include quinolones and coamoxiclav. Administration of steroids is recommended in severely toxemic patients or prolonged illness for a short period of only 2–3 days.

General Measures

These include:

- Isolation of the patient.
- Careful disposal of the excreta.
- Bed rest, good nursing care.
- Attention to maintenance of adequate fluid and dietary intake. A nourishing light fluid or semisolid diet is advisable during the first few days. Rigid dietary regimens are no longer recommended.
- Vitamin and hematinic supplements are often needed in most of the patients.
- Occasionally, blood transfusion (whole blood) is warranted in infants and small children with significant anemia. Blood transfusion is also required in cases of

intestinal and other severe hemorrhages. Surgical intervention may be needed for intestinal perforation.

- Antipyretic agents should be avoided. **Hydrotherapy (tepid sponging)** is the more favored method of treating hyperpyrexia of typhoid fever.
- For eradication of infection in chronic carriers, high dose ampicillin (preferably along with probenecid), given for 4–6 weeks, is recommended. Quinolones may also be effective. Cholecystectomy is indicated in case of failure of drug therapy in chronic gallbladder infection.

Prophylaxis

- Active protection is accomplished by use of **typhoid vaccine** (monovalent and not trivalent) as described in Chapter 10 (Immunization).
- Public health measures constitute the most important and most effective strategy for control of typhoid, however, revolves around.
 - There should be well-organized efforts and planning to improve sanitary conditions and personal, groups, community, food and kitchen hygiene.
 - The public health authorities should ensure clean water supply, proper sewage disposal and control of flies. Education of the public is also of paramount importance.
- Detection and treatment of carriers is another important measure to contain the spread of typhoid fever.

Prognosis

- With adequate treatment, prognosis is generally good. For some unknown reason, it has a more favorable prognosis in children though, in infants, it is rather not quite encouraging.
- Factors adversely affecting the prognosis and causing high morbidity and mortality include:
 - Poor nutritional status
 - Complications such as perforation, severe hemorrhage, meningitis or endocarditis.

In India, mortality rate, on an average, is around 2%. This is a remarkable decline compared to the preindependence figures of 25–50%.

- **Relapse** is said to occur if the individual again develops manifestations of the disease after about 1–2 weeks of stoppage of antibiotic therapy for typhoid fever. It warrants full therapy. Multiple relapses occasionally occur in a single subject.
- **Chronic carrier** state is said to occur if the individual excretes *S. typhosa* for 3 months or more after the attack of typhoid fever. Such subjects have chronic gallbladder infection or chronic urinary carriage, the latter being rare, except in patients with schistosomiasis.

Some authorities recommend giving typhoid vaccine (preferably whole cell killed) after full recovery from typhoid since one attack does not provide solid or long-lasting immunity and, therefore, chance of a second episode, though very low, does exist. It is argued that the child with typhoid is likely to go back to the same environment with continuing risk of another infection.

BRUCELLOSIS

It is also called **undulant fever**, **Mediterranean fever** or **Goat milk fever**; this disease is rare in children in India. It, however, needs to be considered in cases of unexplained pyrexia of prolonged duration, especially with hepatosplenomegaly and lymphadenopathy.

Etiopathogenesis

Brucellosis is caused by Gram-negative organism, *Brucella*, which is known to have at least six species that are transmissible to man.

Infection usually occurs following ingestion of raw milk or one of its products. Following entry into the body, the organisms are phagocytized by leukocytes and monocytes and spread throughout the reticuloendothelial system where they grow further as intracellular parasites. The body responds to the organisms by producing a variety of antibodies. IgM antibodies develop early followed by IgG antibodies which eventually dominate.

Granuloma formation, especially in liver, spleen, lymph nodes and bone marrow constitutes hallmark of the disease. Granulomatous involvement of gallbladder, testes, heart, brain, kidney, bone and skin may also occur.

Clinical Features

Incubation period varies from few days to several months.

- Onset is usually insidious with prodromal symptoms such as weakness, weight loss, exhaustion, anorexia, constipation, headache, muscle pains, etc. With progression of the disease, the child develops high pyrexia, especially toward evening with diaphoresis, abdominal pain, epistaxis and cough.
- Hepatosplenomegaly and cervical and axillary lymphadenopathy are prominent findings. Chest auscultation may reveal crepitations.

Diagnosis

Most useful diagnostic test early in disease is brucella agglutination test showing titers beyond 1:160. Complement-fixation titer of 1:16 or higher is diagnostic later in the course of the disease. Definitive diagnosis is by isolation of the organism in cultures of blood, abscesses or infected tissues.

Treatment

Doxycycline as such or in combination with streptomycin is given for 3 weeks. This is followed by one more 3-week course of doxycycline in combination with cotrimoxazole as also amoxycillin-gentamicin combination have also been used with good results.

Prognosis

Prognosis following specific chemotherapy is excellent.

TUBERCULOSIS

Tuberculosis, caused by *Mycobacterium tuberculosis*, is the most common chronic infectious disease globally. Infants, children and adolescents are most vulnerable to tuberculous infection. Morbidity and mortality too is relatively higher in them. The topic is dealt with in details in See Chapter 26 (Pediatric Pulmonology).

SYPHILIS

Syphilis is caused by a spirochete, *Treponema pallidum*. In congenital syphilis, infection is acquired from the infected mother during the second half of pregnancy. In the relatively rare **acquired syphilis**, infection is acquired through kissing, by sexual contact or through infected nipples. Diagnosis is confirmed by dark-field microscopy and serology (Venereal Disease Research Laboratory {VDRL}). Once a leading cause sexually transmitted disease (STD), syphilis is heading for elimination from India. From 8%, its incidence has come down to 1% in pregnancy. In sex workers, it is around 3–4%. For details on congenital syphilis, turn to Chapter 23 (Intrauterine Infections).

LEPTOSPIROSIS

Definition

Leptospirosis is a zoonotic (spirochete) infection, the causative bacteria finding entry into human through a breach (abrasions and cuts) in skin or mucus membrane exposed to animal excreta (urine).

Etiopathogenesis

The etiologic bacteria is *Leptospira*, a spirochete (Fig. 19.11), which enters the host through a breach in skin. Primarily, *Leptospira* damages the endothelial lining of blood vessels, resulting in ischemic insult to liver, kidneys, meninges and muscles in particular (multiorgan involvement).

Clinical Features

After an incubation period of 7–12 days, **septicemic phase** sets in. During this phase of 2–7 days, organisms can be isolated from blood and CSF. Then, there is a brief period of well-being. This is followed by an **immune phase** (of

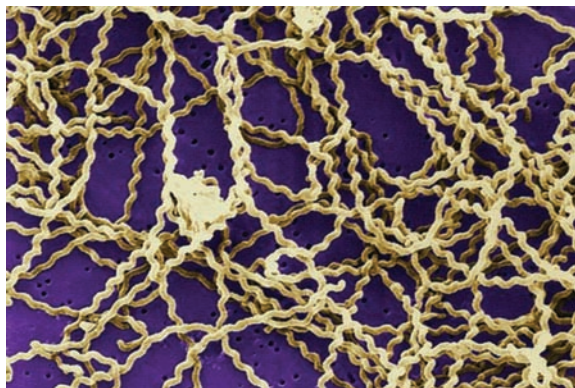


Fig. 19.11: Leptospirosis. Microscopic appearance of the causative bacteria, *Leptospira*, which are long, thin, spiral-shaped motile spirochete.

several weeks) in which organisms disappear from blood and CSF and lodge in tissues. Circulating antibodies appear during this phase. Leptospirosis may be asymptomatic (subclinical) or symptomatic.

- In **symptomatic cases**, onset is sudden, presenting as high fever (70%), aseptic meningitis (20%) or as hepatorenal dysfunction (10%).
- **Mild asymptomatic disease** is anicteric whereas severe disease is icteric (Weil's syndrome).

Differential Diagnosis

It is mainly from febrile illnesses such as dengue, malaria, typhoid, viral hepatitis and UTI. Hantavirus infections may also cause confusion in the diagnosis.

Diagnosis

Diagnosis is confirmed by serology (microscopic agglutination test) which is only infrequently available.

- Dark-field examination of blood—not quite specific
- Blood and/or urine culture
- Serological tests—IgM ELISA, IgM-specific ELISA
- Rapid diagnostic tests. (Two commercially diagnostic kits are available).

Treatment

As soon as the diagnosis is suspected, treatment with parenteral penicillin G (alternatively, tetracycline, doxycycline, provided the child is more than 8 year old) should be initiated.

Prevention

It is in the form of rodent control measures, avoidance of contaminated water and soil, and once a week doxycycline to exposed subjects.

LEPROSY

(Hansen Disease)

Leprosy, caused by *Mycobacterium leprae*, is a chronic granulomatous disease characterized by hypopigmented skin lesions and/or sensory loss from involvement of the nerves.

India is responsible for 25% of the 12 million total cases of leprosy in the world. In the north Indian states, its incidence is far less than in the rest of the country. Unlike adults, early manifestations of leprosy in childhood are often misleading. Generally, it is not diagnosed until the age

of 4–5 years though the child may have been infected much earlier. For details, See Chapter 36 (Pediatric Dermatology).

HELICOBACTER PYLORI (*H. PYLORI*) INFECTION

That infection with *H. pylori* is an important cause of morbidity related to the upper GIT, especially stomach and duodenum, even in pediatric population of underprivileged communities is a recent realization. The topic is discussed in See Chapter 29 (Pediatric Gastroenterology).

RICKETTSIAL INFECTIONS

Rickettsia, a group of Gram-negative microorganisms, occupy a phylogenetical position between viruses and bacteria. Over the years, scrub typhus cases from various parts of India too are on the increase.

Classification

- Spotted fever group
 - *Rickettsia rickettsii* (Rocky mountain spotted fever)
 - *Rickettsia conorii* (Mediterranean spotted fever, Indian spotted fever)
- Transitional group
- Typhus group
 - *Rickettsia typhi* (Murine typhus)
 - *Rickettsia prowazekii* (louse-borne or epidemic typhus) (Fig. 19.12)
- *Orientia tsutsugamushi* (Scrub typhus)
- Ehrlichiosis and anaplasmosis
- *Coxiella burnetii* (Q fever).

Transmission

- **Arthropods:** Ectoparasites like ticks, mites, lice and fleas
- **Animal reservoirs:** Rodents, dogs and cats.

Pathophysiology

Two types of pathology are encountered.

1. **Most rickettsia:** Bite of an ectoparasite produces a skin lesion, eschar. From eschar, the pathology gets localized in the draining lymph nodes. From lymph nodes, it tends to spread systematically. The vasculature of the organs at the endothelial level gets invaded.
2. **Q fever:** Granulomatous lesions.

Clinical Features

Incubation period is 2–14 days. Manifestations of scrub typhus include fever, rash, body pains (headache, myalgia especially of calf muscles), anorexia, malaise, nausea, vomiting, diarrhea, abdominal pain and drowsiness.

The characteristic painless skin rash, eschar (Fig. 19.13), appearing after 2–4 days of illness at the location of the entry of the ectoparasite is usually missed in children. Typically, it appears in the skin folds of axilla, inguinal region, scrotal folds; at times along the line of inner garments. Its size varies between 0.5–2 cm.

Scrub typhus may present with fluid in the third space (ascites, pleural effusion) or pneumonia. In the second week of illness, neurological manifestations may occur.

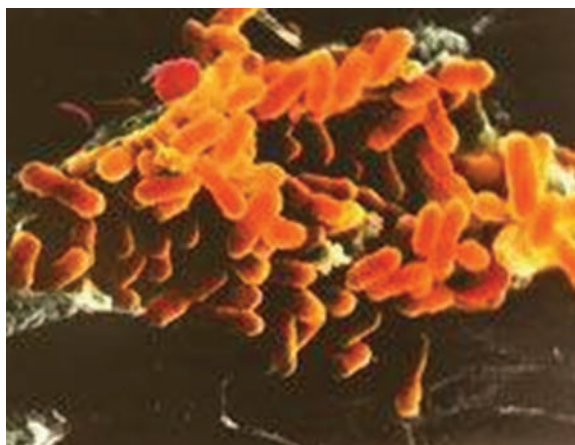


Fig. 19.12: *Rickettsia prowazekii*.

Physical findings include anemia, rash, lymphadenopathy and hepatosplenomegaly.

Diagnosis

High index of suspicion, especially in case scenarios where common conditions do not appear to be the cause of fever is the gateway to diagnosis.

- Investigative findings are nonspecific in the form of leucocytosis or leucopenia, low hemoglobin, thrombocytopenia, hyponatremia and high liver enzymes (aminotransferases).
- Serology (e.g. IgM and antibodies demonstration by immunofluorescence or ELISA) can confirm the specific diagnosis but only in the second week of the illness. Leaving the clinically suspected case untreated for a week or more is neither acceptable nor ethical. The patient's condition can deteriorate and take a worst turn.

Differential Diagnosis

- Exanthematous fever (measles, infectious mononucleosis and Kawasaki disease)
- Complicated malaria
- Dengue
- Meningococemia
- Leptospirosis
- Toxic shock syndrome
- Bleeding diathesis idiopathic thrombocytopenic purpura (ITP), Henoch-Schönlein purpura (HSP),



Fig. 19.13: Eschar. Note the typical skin lesion in rickettsial fever in a young child.

hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP).

Complications

- Acute pulmonary edema
- Pneumonia
- Meningoencephalitis/encephalopathy
- Myocarditis
- Septic shock
- Renal failure
- Vascular collapse.

Treatment

Since diagnosis in a large majority of cases is clinical, empirical therapy is strongly recommended. Doxycycline, 4 mg/kg/day (O, IV) in 2 divided doses, for at least 5–7 days is the therapy of choice. Even if fever subsides earlier, therapy should be given for at least 3 more days. Alternatively, tetracycline, chloramphenicol, azithromycin, roxithromycin or rifampicin may be employed.

Prophylaxis

- Self-protection against mite, louse and ticks is crucial
- Pet dogs need to be disinfected to cut down the population of ticks.

Prognosis

Mortality is high (about 30%).

Multiple Choice Questions

1. All of the following observations about bacterial infections are correct, except:
 - A. Toxic shock syndrome may be caused by *Staphylococcus aureus* and *Streptococcus pneumonia*
 - B. *Haemophilus influenzae* type B infection predominantly occurs in infancy
 - C. Meningococcal vaccine for normal children as a part of routine vaccination is not recommended
 - D. During convalescence from diphtheria, if Schick test is positive, diphtheria toxoid need not be given
2. Drug of choice for pertussis is:
 - A. Erythromycin
 - B. Cefixime
 - C. Ofloxacin
 - D. Ciprofloxacin

contd...

3. Carrier stage in typhoid lasts for:
 - A. Just a month
 - B. 3–4 months
 - C. 1 year
 - D. Indefinite
4. True observations about diphtheria include each of the following, except:
 - A. After near elimination, its cases are again appearing worldwide
 - B. Carrier stage cannot be prevented by DTP vaccine
 - C. Parotitis may occur as one of its complications
 - D. It does not occur in subclinical form
5. None of the following statements are correct, except:
 - A. For fully sensitive and quinolone resistant, severe/complicated typhoid fever, the drug of choice is ceftriaxone
 - B. Currently, recommended therapy for leptospirosis is azithromycin
 - C. The eschar skin lesion is classical of syphilis
 - D. Both maternal and neonatal tetanus are in the last stage of elimination from India

Answers

1. D 2. A 3. D 4. C 5. A

Clinical Problem-solving**Review 1**

RK, an 8-year-old girl presents with 7 days history of continuous pyrexia (becoming remittent with antipyretics and/or tepid sponging), anorexia, abdominal discomfort, constipation and lethargy and hepatosplenomegaly (liver span 10 cm, spleen size grade 4). Dengue and malaria tests as also Widal (done on 5th day of illness) and urine examination negative.

1. What should be the most logical diagnosis in view of the clinical findings and results of investigation?
2. What is the gold standard for diagnosis of this illness?
3. Chloramphenicol, once the drug of first choice for typhoid fever, remained out of use over many years on account of resistant strains. Is there any indication in which it is chloramphenicol that is recommended?

Review 2

An 18-month sick-looking toddler presents with skin lesions which show separation of the areas of superficial epidermis leaving behind denuded areas of skin on a sheer gentle touch and fever.

1. "Skin lesions which show separation of the areas of superficial epidermis leaving behind denuded areas of skin on a sheer gentle touch". What is this clinical sign?
2. In which conditions is this sign positive?
3. What is the most likely diagnosis in this case and why?

Answers**Review 1**

1. Clinically, this girl fits very well in the diagnosis of typhoid fever. Though Widal test is negative, it becomes meaningless since it was done on 5th day of illness when it is expected to be negative even in typhoid fever.
2. Blood/bone marrow culture at any stage of the illness is the gold standard.
3. Today, chloramphenicol remains the drug of choice in fully sensitive uncomplicated cases of typhoid fever.

Review 2

1. Nikolsky sign.
2. Nikolsky sign is positive in toxic epidermal necrolysis (TEN), pemphigus vulgaris and scalded skin syndrome.
3. Staphylococcal scalded skin syndrome (SSS) appears to be the most likely diagnosis in the baby in view of presence of fever and toxic look.

FURTHER READING**JOURNAL ARTICLES/BOOK CHAPTERS/INTERNET**

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INTRODUCTION

Increasing use of antimicrobials, antineoplastic drugs, immunosuppressants and organ transplantation in children have led to the occurrence of invasive fungal infections. These infections, if not appropriately treated, may turn out to be a major cause of morbidity and mortality.

INVASIVE CANDIDIASIS

Etiological Fungus

A yeast-like fungus, candida, has the following main species.

- *Candida albicans*
- *Candida tropicalis*
- *Candida parapsilosis*
- *Candida krusei*
- *Candida glabrata*.

Risk Factors

Vulnerable situations for superinfection with candida include:

- Broad-spectrum antimicrobial therapy
- Prolonged stay in intensive care unit (ICU) (pediatric ICU and neonatal ICU)
- Immunosuppressive therapy
- Very and extremely low birth weight (VLBW, ELBW)
- Renal failure
- Total parenteral nutrition (TPN)
- Central venous (CV) catheters
- Neutropenia.

Clinical Features

Superficial infections manifest in the form of oral thrush, paronychia, vaginitis and colonization at mucosal sites in subjects on antimicrobial therapy. **Invasive candidiasis** manifests, just like bacterial infections, as:

- Sepsis
- Meningitis
- Endocarditis
- Septic arthritis
- Osteomyelitis.

Diagnosis

High index of suspicion clinches the clinical diagnosis. All seriously sick children, especially with immunocompromised status and poor response to appropriate antibiotics, should be reviewed for candidiasis.

Treatment

Antifungal therapy includes amphotericin B, echinocandins and voriconazole.

Prevention

Early treatment with flucazone gives gratifying results.

CRYPTOCOCCOSIS

A fungal disease of humans, most commonly complicating human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) and other immunocompromised states. The increasing number of cases of HIV/AIDS-related cryptococcosis is in keeping with the HIV/AIDS epidemic worldwide, more so in the resource-limited populations.

Etiology

Cryptococcus neoformans is the etiological fungus.

Risk Factors

These include immunocompromised states, especially HIV infection.

Clinical Features

Cryptococcosis involves in order of frequency central nervous system (CNS) (subacute or chronic meningitis), respiratory system (**pulmonary cryptococcosis**) and other systems (**disseminated cryptococcosis**).

- Central nervous system manifestations include nausea, vomiting, headache, meningeal irritation and change in sensorium.
- Pulmonary manifestations include cough, chest pain, weight loss and fever.
- In disseminated form, manifestations depend on the organ(s) involved. Hemolytic anemia and hepatosplenomegaly may be present.

Diagnosis

- **Radiological features:** Diffuse infiltration with hilar lymphadenopathy
- **Serological assay** for immunoglobulin G (IgG) and IgM
- **Serological testing** for cryptococcal polysaccharide antigen by latex agglutination
- **Cerebrospinal fluid (CSF):** It should be for:
 - Increased pressure, cells and protein
 - Demonstration of the fungus as encapsulated yeast cell by India ink

- 376 ■ Cryptococcal antigen testing
- Cryptococcal culture
 - **Definitive diagnosis** by fine needle aspiration cytology (FNAC)/biopsy.

Treatment

- Amphotericin B plus flucytosine × 2–4 weeks or until CSF is rendered negative for *Cryptococcus*. Then, fluconazole alone or amphotericin B should be continued for several (usually 4) weeks.
- Serial lumbar punctures (LPs) for reduction of intracranial pressure (ICP).

ASPERGILLUS SPECIES INFECTION

(Aspergillosis)

Etiological Fungus

The most frequent etiological species are *Aspergillus fumigatus* followed by *A. niger*, *A. flavus* and *A. terreus*.

Risk Factors

- Underlying cancer
- Underlying chemotherapy
- Underlying lung disease
- Prolonged neutropenia
- Immunosuppressive therapy
- Allogenic stem cell transplant (SCT)
- Graft-versus-host disease (GVHD) and its treatment.

Clinical Features

- Manifestations include signs and symptoms in relation to the sites of involvement which usually are sinuses and lungs followed by CNS.
- Invasive manifestations are over and above the noninvasive manifestations such as sinusitis, otomycosis, aspergilloma and allergic bronchopulmonary aspergillosis.

Diagnosis

Diagnosis of *Aspergillus* infection in critically ill children is based on:

- Evaluation of possible risk factors
- Clinical signs
- **Radiological signs:** Chest radiograph shows single or multiple small nodular patches with the halo sign, a zone of low attenuation with a translucent ground glass halo around, a frequent appearing sign in neutropenic patients
- Specific laboratory techniques, especially:
 - Biopsy for histopathological identification of *Aspergillus*, and culture for isolation of *Aspergillus*. This is considered Gold standard by many authorities.
 - Serial estimation of serum galactomannan (GM) and galactomannan index (GMI)
 - Polymerase chain reaction (PCR) and, yet better, quantitative real-time PCR (q-PCR).

Treatment

In view of an extremely high mortality, a sheer clinical suspicion of invasive pulmonary aspergillosis (IPA) is an indication for consideration of initiation of antifungal treatment. Lipid-based preparations of amphotericin B, 3–5 mg/kg/day, are considered a salvage therapy for IPA.

Voriconazole, 6 mg/kg/day in two divided doses on day 1 and 4 mg/kg/day in three divided doses, is the treatment of choice for invasive aspergillosis (IA). Monitoring of plasma drug levels is advisable. Itraconazole is the recommendation in cases refractory to amphotericin B.

Echinocandins like caspofungin is an approved drug for the use of IA refractory to first-line antifungals. Combination of azoles and echinocandins may be used in refractory cases of IA. The duration IPA treatment may last from several months (3 months) to 1 year. Clinical and radiological response is necessary for cessation of treatment. Nonresponders may need surgical resection.

Prognosis

The outcome of IA remains poor with extremely high (60–99%) case fatality rate for cerebral, pulmonary and sinus infections.

MUCORMYCOSIS

(Zygomycosis)

Etiology

Mucorales are responsible for mucormycosis, the third most common invasive fungal infection. These organisms are ubiquitous saprophytes in nature rarely infecting organs with intact immune system. Based on anatomic location, mucormycosis is classified in six forms:

1. Rhinocerebral
2. Pulmonary
3. Cutaneous
4. Gastrointestinal
5. Disseminated
6. Uncommon presentations.

All patients with chronic infection of the paranasal sinuses, burns or traumatic wound infection should have their skin meticulously examined for the presence of either black discoloration or black eschars.

Mucormycosis in the ICU setting is related more commonly to massive injuries, e.g. motor vehicle accidents, natural disasters or complex combat trauma. Sporadic mucormycosis is a life-threatening condition, almost always associated with certain risk factors, mainly neutropenia and prolonged acidosis, either diabetic or renal origin.

Diagnosis

Diagnosis is based on:

- Histopathology of tissue samples. Stains showing characteristic broad nonseptated hyphae, irregularly branched at angles varying from 45°–90° are pathognomonic.

- Cultures of the fungus.
- Computed tomography (CT) chest may identify infiltrates suggestive of mucorales that are not seen on chest X-ray.

Management

- Antifungal therapy using amphotericin B intravenously (IV) for 6 weeks
- Reduction in immunosuppressive therapy
- Surgical debridement
- Treatment of underlying medical condition.

HISTOPLASMOSIS

Histoplasmosis is an acute progressive, life-threatening infection in children.

Etiological Fungus

The dimorphic fungus, *Histoplasma capsulatum*, is the causative fungus.

Clinical Features

- Manifestations include prolonged fever, cough, weight loss, abdominal pain, hepatosplenomegaly, lymphadenopathy and skin lesions.
- Neurological presentation, as and when it occurs, is in the form of meningoencephalitis with or without focal neurological deficits.

Diagnosis

- Fungal stain (on blood/tissue)
- Rapid antigen detection in urine has better sensitivity than in blood to diagnose invasive histoplasmosis
- Blood culture is diagnostic.

Treatment

Immunocompetent children need no treatment. Amphotericin B is the drug of first choice for invasive disease in immunosuppressed children. For long-term suppressive therapy, itraconazole should be employed.

Multiple Choice Questions

- Spot the wrong observation:
 - Among the risk factors for invasive candidiasis figure immunocompromised status, total parenteral nutrition, neutropenia, therapy with broadspectrum antibiotics, etc
 - Invasive candidiasis may manifest like sepsis
 - Disseminated cryptococcosis is most common among various cryptococcosis
 - Neurological manifestation of histoplasmosis is in the form of meningoencephalitis
- True observations about aspergillosis include each of the following, except:
 - Cancer chemotherapy, lung disease and cancer are the risk factors
 - Voriconazole is the drug of choice for invasive aspergillosis
 - Allogeneic stem cell transplant (SCT) is a risk factor
 - Biopsy is no longer considered the gold standard for its diagnosis
- True observations about cryptococcosis include each of the following, except:
 - Usually complicates immunocompromised states including HBV/AIDS
 - Cryptococcus neoformans* is the etiological fungus
 - Definitive diagnosis is by serology
 - Initial therapy is amphotericin B plus flucytosine × 2–4 weeks or until CSF is rendered negative
- True observations about aspergillosis include each of the following, except:
 - The most frequent etiological species are *Aspergillus fumigatus* followed by *A. niger*, *A. flavus* and *A. terreus*
 - Manifestations remain nearly fixed regardless of the location of the lesion(s)
 - Demonstration of the fungus as encapsulated yeast cell by India ink
 - In view of an extremely high mortality, a sheer clinical suspicion of invasive pulmonary aspergillosis (IPA) is an indication for consideration of initiation of antifungal treatment
- True observations about mucormycosis include each of the following, except:
 - The third most common invasive fungal infection
 - Diagnosis is based on histopathology and culture
 - Sporadic mucormycosis is a mild condition
 - Antifungal drug, amphotericin B is the drug of choice
- Each of the following is incorrect, except:
 - Increasing use of antimicrobials, antineoplastic drugs, immunosuppressants and organ transplantation in children have led to the hike in occurrence of invasive fungal infections
 - Surgical debridement has no role
 - All sick children should be reviewed for candidiasis
 - Itraconazole is the drug of first choice for invasive disease in immunosuppressed children

Answers

1. C 2. D 3. C 4. B 5. C 6. A

Clinical Problem-solving

Review 1

A 2-year-old girl suffering from X-ray established right upper lobe consolidation with pneumatocele along with septic arthritis of both knees shows poor response to ampicillin-cloxacillin followed by vancomycin over 5 days period. At this stage, oral and vulvo-vaginal thrush is noticed.

1. What could be this child's problem that is refractory to proper antibiotics administered over 5 days period?
2. What other complications are likely in this child?
3. Would you suggest a modification in therapy?

Review 2

A 13-year-old teenager, a known case of cystic fibrosis on replacement and supportive therapy, develops malodorous discharge, inflammation, pruritus, scaling, and severe discomfort. In right external ear which is diagnosed as otomycosis by ENT specialist. While he is being investigated, his respiratory status worsens with severe cough, breathlessness, chest pain and fever. CXR shows multiple small nodular patches with the halo sign.

1. What is your clinical diagnosis and why?
2. How can the diagnosis be confirmed?
3. Can treatment be started even before confirmation of diagnosis?
4. What is the recommended treatment?

Answers

Review 1

1. Clearly, this girl's problem is not restricted to bacterial pneumonia and septic arthritis (most likely staphylococcal). The poor response to appropriate antibiotic therapy along with new evidence of oral superficial thrush (oral and vulvo-vaginal) points to the probability of invasive candidiasis.
2. Left without additional treatment, she may develop meningitis, endocarditis, osteomyelitis, etc.
3. Yes, she needs to be treated with antifungal drugs such as amphotericin B, echinocandins and voriconazole.

Review 2

1. Invasive pulmonary aspergillosis in view of pulmonary manifestations, evidence of fungus infection in the external ear, suggestive chest X-ray and predisposing cystic fibrosis in this boy.
2. Biopsy, serial estimation of serum galactomannan (GM) and galactomannan index (GMI) PCR/real-time PCR (q-PCR).
3. Yes, treatment can be started even before confirmation of diagnosis in view of nature of the disease.
4. Voriconazole, 6 mg/kg/day in two divided doses on day 1 and 4 mg/kg/day in three divided doses, is the treatment of choice for invasive aspergillosis. As salvage therapy, amphotericin B (lipid-based) should be used as salvage therapy.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

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2. Steinbach WJ, Benjamin DK. Neonatal candidiasis. *Infect Dis Clin North Am* 2005;19:603–615.
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BOOK

1. Huxley E, Lucy A. *Fungus Infections*. Philadelphia: Academecia 2013.

MALARIA

Malaria (*mala* meaning bad and *aria* meaning air) is a protozoal infection, characterized by recurrent fever, splenomegaly and anemia. It is the most persistent, the most destructive, the most widespread and the most difficult to control among all the tropical ailments. Until the beginning of 1970s, it had virtually disappeared from India. Ever since 1971, it has returned to India and other Southeast Asian countries with a big bang.

Etiology

Malaria is caused by the malarial parasite. Its four types in order of frequency of occurrence in India are—(1) *Plasmodium vivax*, (2) *P. falciparum*, (3) *P. malariae* and (4) *P. ovale*.

The most common strain of malarial parasite responsible for the disease in India and most other tropical and subtropical countries is *P. vivax* (which causes benign tertian malaria) followed by *P. falciparum* (which causes malignant tertian malaria). In some parts of India and Africa, *P. falciparum* is the dominant type. *P. ovale* and *P. malariae* (not seen in India) clinically behave just like *P. falciparum*. Transmission occurs through the bite of a female anopheles mosquito. Sexual cycle of the parasite is completed in the mosquito per se, but asexual cycle occurs in the humans.

Life Cycle

Life cycle of malarial parasite is shown in Figure 21.1. **Pre-erythrocytic (hepatic or tissue) phase** follows the bite. Within 30 minutes, the sporozoites move from blood into the liver and the reticuloendothelial tissue. Those escaping destruction by phagocytes reach the hepatocytes where they undergo an asexual reproduction. Over a variable number of days (8 and 5.5 in *P. vivax* and *P. falciparum*, respectively), thousands of merozoites are formed in the hepatic or tissue schizont which then ruptures to release merozoites into the circulation. In this phase (in other words the incubation period), the subject is asymptomatic.

Erythrocytic phase starts with the invasion of erythrocytes by merozoites. The merozoite once within the erythrocyte is called **trophozoite** which takes the shape of a signet ring. The latter transforms to an ameboid form. Then, there is a dividing stage (erythrocytic schizont) in which the nucleus of the ameboid form divides into 20 or more merozoites. The infected erythrocyte finally ruptures, releasing merozoites into the circulation. These merozoites are capable of invading fresh erythrocytes and causing further cycle. In this phase, the subject becomes symptomatic

with paroxysms of high pyrexia. The pigmentation of various organs, hyperplasia of reticuloendothelial system and late effects like anemia and fatty degeneration are the outstanding pathologic features of the disease.

Sexual reproduction follows when, after many stages of schizogony, some merozoites transform into sexual stages (the male microgametocytes and the female macrogametocytes) within the erythrocytes. When the patient is bitten by the female anopheles mosquito at this particular stage, it sucks the infected blood. In the mosquito's stomach, all forms except gametocytes get destroyed. As a result of some structural changes, the gametocytes become gametes. The male microgamete penetrates the female macrogamete. The fertilized macrogamete is called **zygote**. The zygote is called **ooocyte** when it rests below the outer cell layer of the mosquito's stomach. When the oocyte ruptures, it releases sporozoites into the body cavity of the mosquito. On migration to the salivary glands, these sporozoites are ready to be released in the blood of the human host following the mosquito bite.

Epidemiology

Humidity and rainfall increase the spread of the disease. Malaria shows peak prevalence in warm and humid environment. Maximum cases are, therefore, seen in July to November in India.

Most conducive sites for the parasite are stagnant water, pools, ponds, marshy areas, burrowed pits and poorly or unregulated irrigation channels. Low plasma vitamin A status is associated with increased risk of *P. falciparum* parasitemia, leading to increased morbidity and mortality, perhaps by disruption of normal immunological function for which vitamin A is vital. Higher the altitude, less the chance of malaria. Above 2000 meters altitude, it is infrequent to have this disease.

Certain hemoglobinopathies are protective and tend to be genetically selective in endemic malarious region. *P. falciparum* may fail to mature in children with sickle cell trait and *P. vivax* in those with thalassemia and enzyme deficiencies; glucose-6-phosphate dehydrogenase (G6PD) deficiency. *P. falciparum* is unable to attain high density in children with G6PD deficiency. In order to evaluate prevalence of malaria in a community, three epidemiological parameters are available (Box 21.1).

Host Response

Initially, the host responds to malarial infection by activating nonspecific defense mechanism resulting in accelerated

i = Infective stage
d = Diagnostic stage

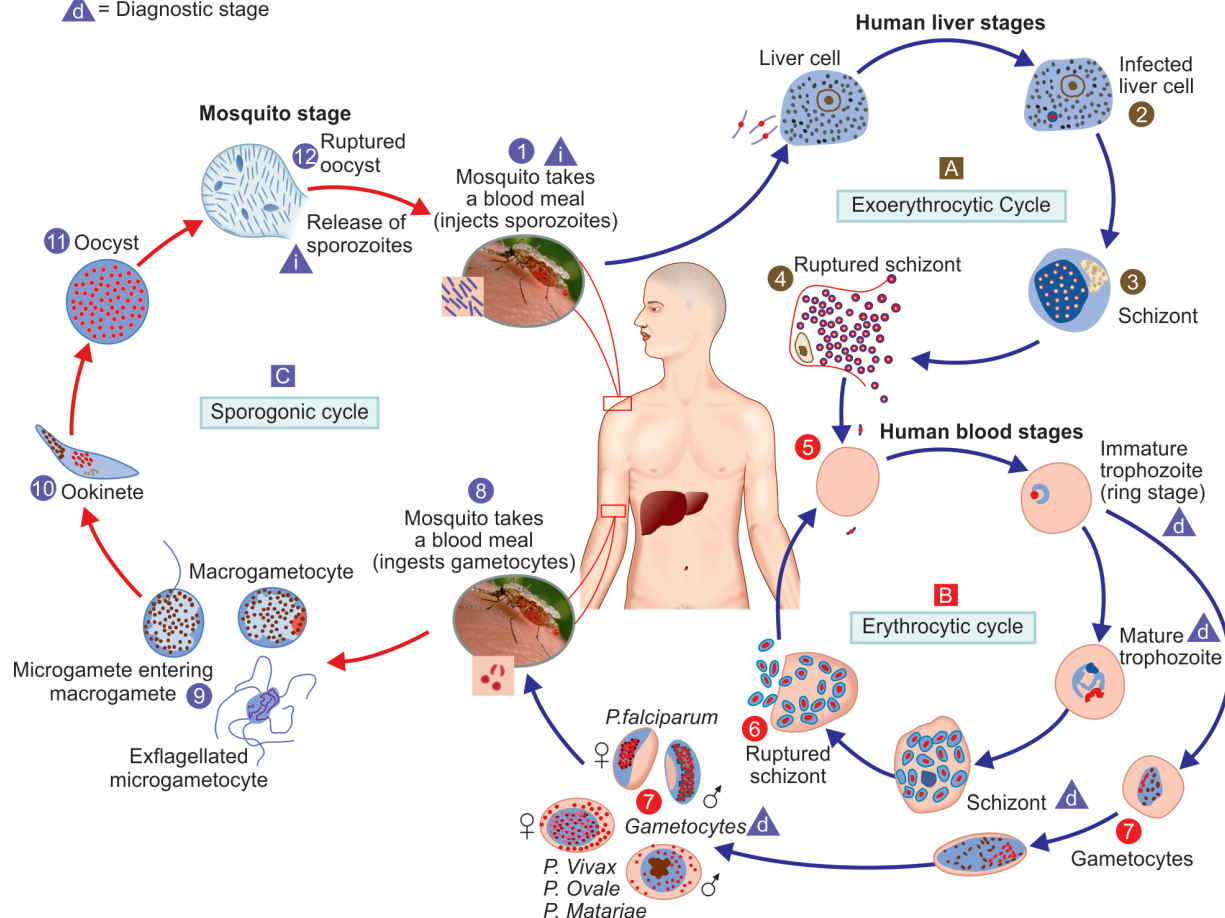


Fig. 21.1: Malaria. Life cycle of malarial parasite.

Source: Center for Disease Control and Prevention, Atlanta.

Box 21.1

Three epidemiological parameters for evaluating prevalence of malaria in a community

1. **Splenic index** is measured by the rate of palpability of spleen in the age group 2–10 years. The area is designated as **holoendemic** if the splenic rate is over 75%, as **hyperendemic** if the rate is over 50% and **low prevalence** if the rate is under 10%.
2. **Parasitic rate** is the percentage of positive blood films in 2–10 years age group.
3. **Proportionate case rate** is the number of clinically diagnosed malaria cases for every 100 subjects examined in a clinic. This is merely a crude estimate of prevalence of malaria.

destruction of parasitized and nonparasitized erythrocytes. Those infected cells that escaped splenic removal are destroyed when schizont ruptures. The material released induces the activation of macrophages and release of cytokines which causes fever and exert other pathological effects. Temperature of 40°C is schizontocidal. In untreated infections, the effect is to synchronize the parasitic cycle with eventual production of regular fever spikes and rigors that originally served to characterize the different malaria.

The specific immunity to malaria eventually controls the infection and confers protection from high level parasitemia and disease, but not from infection. As a result, asymptomatic

parasitemia is common in older children living in holoendemic or hyperendemic areas.

Both cellular and humoral immunity are necessary. Immune children have a polyclonal increase in serum levels of IgM, IgG and IgA. Passively transferred IgG from immune individuals has been shown to reduce parasitemia in children and in infant upto 1 month.

Several factors delay the development of cellular immunity, including the absence of major histocompatibility antigens on the surface of infected red blood cells (RBCs) which preclude direct T cell recognition; malaria antigen specific immune unresponsiveness and the strain diversity along with the ability of the parasite to express immune dominant variant antigens on erythrocyte surface that change during the period of infection.

Pathogenesis

The pathological changes in malaria are mainly due to invasion of erythrocytes by parasites resulting in hemolysis. The hemolysis often leads to increase in serum bilirubin. Sometimes, it is severe enough (particularly in *P. falciparum*) to result in hemoglobinuria (**blackwater fever**).

Anemia is common and is mainly due to invasion and destruction of RBCs and partly due to dyserythropoiesis, quinine therapy and immune hemolysis. The released pig-

ments accumulate in the reticuloendothelial cells of splenic follicles resulting in hyperplasia, in Kuffer cells of liver, bone marrow, brain and other organs. The deposition of pigment and hemosiderin results in slate gray color of the organs.

In *P. falciparum* infections, sequestration of large number of parasites occurs in the venules and capillaries of various organs and lead to tissue dysfunction. Sequestration is due to ability of parasites to induce changes in erythrocyte surface and causing them to adhere to endothelial cells. Three receptors: (1) intracellular adhesion molecule-1 (ICAM-1), (2) cluster of differentiation (CD) 36 and (3) thrombospondin have been identified for parasitized erythrocytes and for causing cerebral damage. Host cytokines also make endothelial cells more adhesive for the surface of parasitized red cells, thus augmenting sequestration. The large number of actively metabolizing parasites consumes oxygen and glucose or produce toxic metabolites including lactate that may affect cellular function. The sequestration also stimulates release of host transmitter including nitric oxide that may have a local effect on blood or the conduction of nerve impulses.

Thrombocytopenia and spontaneous bleeding may occur and may be associated with disseminated intravascular coagulopathy (DIC). The capillaries and mesangium of kidney contain deposits of immunoglobulins, complements and malarial antigens resulting in transient acute diffuse glomerulonephritis which usually resolve by appropriate antimalarial therapy.

Clinical Features

Incubation period varies from 9 days to 30 days. *P. falciparum* has the lowest whereas *P. malariae* has the highest incubation period. Clinical manifestations depend upon the type of infecting species and resistance or immunity of the host. Classically, three stages are described:

1. **Cold stage:** Chills, rigors, nausea, headache, anorexia and malaise
2. **Hot stage:** Dry flushed skin, remarkable thirst and rapid respiration
3. **Sweating stage:** Fall in temperature by crisis.

This classical pattern so characteristic of adult malaria, usually is absent in children less than 5 years of age. It may or may not occur in older children.

- High fever with headache, restlessness, anorexia, malaise, sweating and failure to eat or drink are the most common mode of presentation in infants and children.
- Chills and rigors, which are considered to be the hallmark of malaria in adults, are only uncommonly encountered in infancy and early childhood.
- Fever may be remittent or continuous rather than intermittent.
- Even fever and other significant symptoms may be absent in some children with massive parasitic load in their blood.
- Diarrhea, vomiting, pain in abdomen, convulsions and even coma may be present in some of the children.



Fig. 21.2: Malaria. Note the hepatosplenomegaly in a 9-year-old girl. In addition to intermittent high fever, she had moderate anemia and growth retardation.

- Progressive pallor (anemia) and hepatosplenomegaly (Fig. 21.2) are usually present; the enlargement of spleen being more predominant.
- Petechial hemorrhage in skin or mucus membranes develop only rarely in severe falciparum malaria.

Neonatal malaria is uncommon in endemic areas because of the transplacental passage of maternal antibodies (IgG). When it occurs, the cause may be transfer of infection from mother (congenital malaria), an infected blood transfusion or natural infection. In falciparum malaria, presentations are similar to that caused by other species, but complications are more common.

Complicated or severe malaria is the term applied to cases that have one or more of the features given in Table 21.1. The important manifestations of severe malaria in children are altered consciousness, labored breathing and severe anemia which may occur singly or in combination. Hypoglycemia may occur and is associated with increased mortality. Renal failure, pulmonary edema and DIC are less likely to develop in children.

Chronic malaria is the term applied to repeated attacks of malaria leading to growth retardation, anemia and hepatosplenomegaly. **Relapse** is the term applied to recrudescence of pyrexia after a gap that is more than the normal periodicity of malarial pyrexia. Relapses are common in *P. vivax* infection but rare in *P. falciparum* infection which is devoid of exoerythrocytic phase.

Complications

Cerebral Malaria

It is characterized by coma which cannot be explained by hypoglycemia or a transient postictal state and absence of other causative disease in a child with falciparum malaria. If untreated, it is associated with death rate of approximately 20% in children. The onset may be gradual or sudden.

Majority of children have fever, irritability and listlessness prior to loss of consciousness. Convulsions are common and sometimes herald the onset of coma. Vomiting, cough and diarrhea may occur. Respiration is rapid; in some breathing is stertorous. Jaundice may be present.

Table 21.1: Complicated (severe) malaria: Clinical and laboratory criteria/features as per WHO

Clinical criteria/features	Laboratory criteria/features
<ul style="list-style-type: none"> • Impaired consciousness/arousable coma • Prostration (inability to sit up/walk without assistance) • Multiple convulsions (>2 episodes in 24 hours) • Shock/circulatory collapse (systolic BP <50 mm Hg) • Jaundice plus evidence of other vital organ dysfunction • Hemoglobinuria • Spontaneous bleeding • Radiological evidence of pulmonary edema 	<ul style="list-style-type: none"> • Hypoglycemia (blood sugar <40 mg/dL) • Metabolic acidosis (plasma bicarbonate <15 mEq/L) • Severe normocytic anemias (hemoglobin <5 g/dL; hematocrit (PCV) <15%) • Hemoglobinuria • Hyperparasitemia (>2% or 100,000/μL in areas of low intensity transmission, or >5% or 250,000/μL in areas of high stable malaria transmission intensity) • Hyperlactatemia (lactate >5 mmol/L) • Renal; impairment (serum creatinine >265 μmol/L)

Abbreviations: WHO, World Health Organization; PCV, packed cell volume; BP, blood pressure.

Liver may be moderately enlarged and spleen may be palpable. Some children may develop a shock like state with hypotension, cold extremities and a wide core to skin temperature difference.

In cerebral malaria, there is diffuse symmetric encephalopathy; focal neurological signs are unusual. Although some degree of resistance to head flexion may be present, signs of meningeal irritation are lacking. Eyes may be divergent and a pout reflex is common but other primitive reflexes are usually absent. Pupillary reflex and corneal reflex are preserved except in deep coma. Brain stem reflexes are also lost. Muscle tone may be either increased or decreased. Tendon reflexes are variable and plantar reflexes may be flexor or extensor. Abdominal reflexes are invariably absent. Decerebrate or decorticate posture may be present. Patients may have retinal hemorrhages (15%). Less than 5% of patients have significant bleeding or other clinical evidence of DIC. Convulsion, usually generalized and repeated, is common. Approximately 10% of surviving children may have neurological deficit.

Hypoglycemia

It is common and associated with poor prognosis. It is due to failure of hepatic gluconeogenesis and increase in consumption of glucose by both host and parasites. Furthermore hypoglycemia is aggravated by quinine therapy. This manifests as sweating, breathlessness, tachycardia, deteriorating consciousness, seizures, extensor posturing, shock and coma.

Lactic acidosis commonly coexists with hypoglycemia in patients of malaria. Anaerobic glycolysis in tissues, lactate production by parasites and failure of hepatic lactate clearance are usual causes of lactic acidosis. Other contributory factors for acidosis are dehydration, shock, repeated seizures and hypoglycemia.

Noncardiogenic Pulmonary Edema

The exact cause of this is not known. It can be aggravated by vigorous administration of intravenous (IV) fluid and increased capillary pulmonary permeability. Manifestations are tachypnea, dyspnea and hypoxia.

Renal Impairment

Renal impairment is common with severe falciparum malaria. The exact pathogenesis is not known but may

be related to sequestration of renal microcirculation with parasitized erythrocytes. The lesions resemble acute tubular necrosis (ATN). Renal cortical necrosis never occurs. This is manifested as oliguria, anuria and increase in serum blood nitrogen and creatinine.

Coagulation Abnormalities

These are common in falciparum malaria. Less than 5% of patients with severe malaria have significant bleeding with evidence of DIC. Hematemesis, probably from stress ulcer or acute gastritis may also occur.

Aspiration pneumonitis following convulsion is an important cause of death in cerebral malaria. Malaria predisposes to bacterial superinfection possibly through its effect on immune response. Chest infections and catheter-related urinary tract infection (UTI) are common. Spontaneous Gram-negative septicemia develops occasionally in severe malaria.

Black Water Fever

This is due to sudden, severe, massive, intravascular hemolysis and manifested clinically as passage of coca colored urine. The color of urine is due to hemoglobinuria. Renal failure may supervene. This condition occurs in children with G6PD deficiency. Hypersensitivity to antimalarial drug is the most likely cause.

Algid Malaria

Dehydration, Gram-negative septicemia and, rarely, hemorrhage, may cause peripheral circulatory failure (shock) with cold clammy limbs.

Quartan Malarial/Nephropathy

Chronic or repeated infection with *P. malariae* may cause soluble immune complex injury to the renal glomeruli resulting in nephritic syndrome. The histopathological appearance is that of focal or segmental glomerulonephritis with splitting of the capillary basement membrane. Subendothelial dense deposits are seen on electron microscopy and immunofluorescence reveals deposits of complement and Ig. The response to therapy is poor with either antimalarial agents or glucocorticoids and cytotoxic drugs.

Malaria related immunosuppression provokes infection with lymphoma virus; Epstein-Barr virus. Burkitt's lymphoma is strongly associated with this virus.

Tropical Splenomegaly

Moderate to massive splenomegaly occurs as an immunological response to exposure to repeated malarial infections in endemic and hyperendemic areas. This is discussed *vide infra*.

Differential Diagnosis

The differential diagnosis is usually from dengue, typhoid fever, tuberculosis, influenza, UTI, septicemia, liver abscess and hepatitis, etc.

Diagnosis

High degree of suspicion in children with the above clinical picture is of paramount importance in the diagnosis, especially in our set-up. In fact, it is a sound policy to exclude malaria in all cases of pyrexia of doubtful origin in the tropics.

Peripheral Blood Film

The positive peripheral smear (thick for identifying the parasite and thin for recognizing its type) usually clinches the diagnosis (Fig. 21.3). However, blood film for malaria parasite has a failure rate of a high magnitude since it is seldom repeated at intervals of 12 hours following the negative outcome of the film made earlier and since it is often not properly prepared and/or carefully examined (Box 21.2).

Bone Marrow

Occasionally, bone marrow smear may be required when peripheral smear is negative, but there remains a high suspicion of the disease.

Quantitative Buffy Coat Test

Quantitative buffy coat test is a fast, more sensitive and easy, but expensive method for identifying malarial parasite. It consists of examining the blood film (stained with acridine orange) under ultraviolet light source.

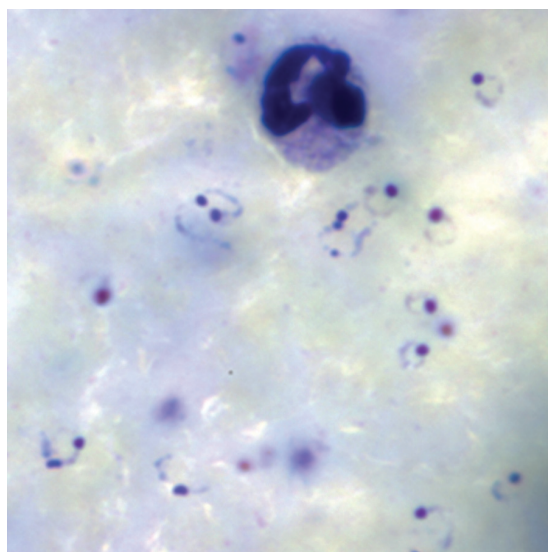


Fig. 21.3: Malarial parasite. Note the ring-shaped malarial parasite (*P. falciparum*) in peripheral blood film.

Box 21.2

Factors contributing to false-negative microscopy in malaria

- Less number of fields examined (recommendation is at least 100 fields)
- Seldom repeated after 12 hours following the negative outcome as per standard recommendation. A minimum of 3 smears at 6–8 hour gap in highly suspected cases is needed.
- Immunocompromised state
- Massive parasitemia causing sequestration
- Partially-treated malaria.

Box 21.3

Recommended investigations for assessment of severity and management of pediatric malaria

- **Blood:** CBP, blood sugar, electrolytes, pH, bicarbonate, chloride and lactate, PT, PTT, bilirubin, transaminases, creatinine; culture
- **Urine:** Hemoglobinuria
- **Chest X-ray:** To exclude pulmonary edema (ARDS)
- **CSF analysis:** LP should be considered in the presence of a febrile encephalopathy if *P. falciparum* is not identified as its cause.

Abbreviations: CBP, Complete blood picture; PT, prothrombin time; PTT, partial thromboplastin time; ARDS, acute respiratory distress syndrome; CSF, cerebrospinal fluid; LP, lumbar puncture.

Fluorescent Antibody Technique

It may be employed for detecting species specific IgG antibodies which are known to persist for many months after cure of malaria.

Rapid Diagnostic Test

Three such tests are in vogue at present:

1. **OptiMAL strip test** which is based on detection of parasite lactate dehydrogenase (LDH)
2. **Plasmodium aldolase test**
3. **Parasight F test** which is based on detection of histidine-rich protein 2 (HRP2) antigen of *P. falciparum*.

Polymerase Chain Reaction (PCR)

This exceedingly sensitive and specific test for all species of malaria is of value even in a case scenario with low level of parasitemia. As yet, it is employed for research purposes only and is not available for routine use. Over and above test(s) for confirmation of clinical diagnosis, patients need to be evaluated for severity of the illness and its management through additional investigations (Box 21.3).

Treatment

Uncomplicated Vivax Malaria

Specific treatment consists of administering the anti-malarial drugs as soon as possible after the diagnosis is confirmed. The drug recommended by the World Health Organization (WHO) and adopted by the National Vector-borne Disease Control Program continues to be chloroquine. The regimen of administering chloroquine consists of 10 mg/kg (in terms of base) followed by 5 mg/kg 6 hours later. The dose of 5 mg/kg is again given on the second day as well as the third day. Thus, the doses are at 0, 6, 24 and 48 hours (first 10 mg/kg; others 5 mg/kg each; a total of 25 mg/kg).

384 Alternatively, amodiaquine may be given in same dosage as in case of chloroquine. A combination of 500 mg sulfamethopyrazine (SMP) or sulfadoxine and 25 mg pyrimethamine, given in a dose of 25 mg/kg with reference to SMP or sulfadoxine, is recommended in resistant cases. Cases failing to respond to chloroquine and sulfa-pyrimethamine combination need to be treated with alternative drugs like mefloquine, artemisinin derivatives or halofantrine. Even cotrimoxazole may be employed in such cases.

Primaquine, 0.25–0.3 mg/kg/day for 14 days, should be given as a radical therapy in order to eliminate exoerythrocytic stages in liver, thereby cutting down risk of relapse. Primaquine may result in hemolytic anemia in G6PD deficiency individuals. It is, therefore, desirable (though not essential) to screen the patient for G6PD before administering this agent.

Uncomplicated *Falciparum* Malaria

WHO now categorically recommends artemisinin-based combination therapy (ACT) in even uncomplicated *P. falciparum* malaria. Presently, the best and most commonly employed ACT is artemether plus lumefantrine available as tablets. Primaquine, 0.75 mg/kg/day (O) once only, should be given in *P. falciparum* malaria to safeguard against community transmission through its gametocidal action.

Uncomplicated Mixed Malaria

The recommendation for uncomplicated *P. falciparum* malaria, as specified earlier, should be followed.

Complicated (Severe) Malaria

Treatment of complicated (severe) malaria, no matter it is vivax or falciparum, is on the same lines, invariably employing parenteral therapy.

Artemisinin-Based Regimen

Artemether, a semisynthetic derivative of artemisinin, has now emerged as the best drug for cerebral and other types of severe malaria. The drug has a rapid onset of schizonticidal action, the parasite clearance time being 24–36 hours. It is available as 80 mg ampoules.

Its total dose is 9.6 mg/kg intramuscularly (IM)—3.2 mg/kg on first day and 1.6 mg/kg/day on subsequent 4 days. Alternatively, it may be given in the dose of 3.2 mg/kg stat, after 12 hours and 24 hours followed by daily dose on 3 successive days. Artesunate is given in dose of 2.4 mg/kg stat, after 12 hours and 24 hours followed by daily dose on 3 successive days.

Adverse drug reactions (ADRs) include nausea, vomiting, abdominal discomfort, reduced leukocyte and reticulocyte count, increased transaminase (aspartate transaminase {ASAT}, alanine transaminase {ALAT}), bradycardia and arterioventricular block. Along with artemether or artesunate, lumefantrine should also be administered.

Quinine-based Regimen

Quinine IV infusion is still considered the therapy of choice in cerebral malaria by some authorities. The dose is 10 mg/kg. It should be dissolved in 200 mL of saline and given as IV drip

slowly in 2–4 hours. This should be repeated 12 hourly until 6–8 doses are given.

To achieve therapeutic levels at the earliest, a loading of 20 mg/kg in 10 mL/kg of normal saline or dextrose over 4 hours may be administered at the outset. Subsequently, the normal 10 mg/kg quinine infusion over 2 hours should be continued every 8 hourly.

The occurrence of reactions such as convulsions, delirium, confusion, coma and hypotension is an indication for discontinuing the infusion. As a policy, IV quinine should be switched over to oral quinine at the earliest, usually after 24 hours. On an average, a total of 7 day course is required. IM quinine can be employed but the outcome is not as satisfactory as with IV infusion.

ADRs of quinine include bitter taste, nausea, vomiting, tinnitus, deafness, headache, visual disturbances (the so-called *cinchism*). Serious ADRs include prolonged QTc interval in electrocardiogram (ECG), hypoglycemia, intravascular hemolysis, blackwater fever and immune mediated thrombocytopenia, etc.

General measures include:

- Good nursing care
- Maintenance of adequate fluid and nutritional balance
- Maintenance of hemodynamic stability
- Use of antipyretics for fever and anticonvulsants for seizures
- Treatment of anemia and other associated deficiencies must receive attention at the earliest
- In order to reduce cerebral edema, it is advisable to give dexamethasone, 3 mg/kg IM every 6 hours
- In case of acute renal failure, restriction of fluids, salt and protein in diet is needed
- Hemoglobinuria warrants injectable sodium bicarbonate for alkalinizing the urine as also blood transfusion for the accompanying anemia
- In case of worsening renal failure, peritoneal dialysis is indicated.

Prognosis

It is generally good, provided treatment is initiated soon. In the absence of complications, it becomes difficult to predict the outcome. Malnutrition and other associated illness have adverse effect on prognosis. WHO's guidelines of poor prognostic indicators are given in Box 21.4.

Prophylaxis and Control

- **Vector control:** It is important to control mosquito vector by measures including insecticides such as dichlorodiphenyl trichloroethane (DDT), elimination of breeding places, space fogging, biological control (larvivorous fish in water bodies). The **Roll-back malaria initiative** (WHO, United Nations Children Emergency Fund {UNICEF}, United Nations Development Programme {UNDP}, World Bank), launched in 1998, is actively in operation.
- **Early case detection and prompt treatment** with chloroquine in uncomplicated vivax and artemisinin derivatives or quinine in falciparum malaria and all severe malaria regardless of the species.

Box 21.4**Indicators of poor prognosis in malaria as per WHO****Clinical indicators**

- Age under 3 years
- Deep coma
- Witnessed or reported convulsions
- Absent corneal reflex
- Decerebrate/decorticate rigidity
- Clinical signs of organ dysfunction (renal failure, pulmonary edema)
- Respiratory distress (acidosis)
- Circulatory collapse
- Papilledema and/or retinal edema.

Laboratory indicators

- Hyperparasitemia ($>250,000/\mu\text{L}$ or $>5\%$)
- Peripheral schizothemia
- Peripheral blood polymorphonuclear leukocytosis ($12,000/\text{mm}^3$)
- Mature pigmented parasites ($>20\%$ of parasites)
- Peripheral blood polymorphonuclear leukocytes with visible malarial pigment (5%)
- Packed cell volume less than 15% or Hb: $<5\%$
- Blood glucose less than 2.2 mmol/L (40 mg/dL)
- Blood urea more than 60 mg/dL
- Serum creatinine more than 3.0 mg/dL
- High lactic acid (>6 mmol/L)
- Low CSF glucose
- Raised venous lactic acid (>5 mmol/L)

More than three-fold elevation of serum enzymes (ALT, AST)

- Increased plasma 5'-nucleotidase
- Low antithrombin III levels
- Very high plasma concentrations of TNF.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; TNF, tumor necrosis factor; CSF, cerebrospinal fluid; WHO, World Health Organization; Hb, hemoglobin.

- **Suppressive therapy:** One or two tablets of chloroquine phosphate every week to all those exposed to malaria in endemic areas during epidemics is considered to be of considerable value in prophylaxis.
- **New approaches:**
 - Vaccine—malaria vaccine is still not ready for clinical use
 - Gene therapy
 - Gene mapping
 - Low interleukin-12.

TROPICAL SPLENOMEGALY

(Big Spleen Disease, Bengal Splenomegaly, Cryptogenic Splenomegaly, Idiopathic Splenomegaly Syndrome)

Definition

Tropical splenomegaly is the name applied to an etiologically obscure **chronic splenomegaly** (moderate to massive) together with hepatomegaly, **undernutrition and anemia**, encountered in children, adolescents and young adults in hyperendemic and holoendemic malarial regions of tropics and subtropics without an obvious cause.

Marked elevation in serum titers of IgM and malarial antibody, hepatic sinusoidal lymphocytosis and peripheral B cell lymphocytosis are present.

Etiopathogenesis

According to current hypothesis, the entity is an abnormal immune response to repeated infections with malaria in hyperendemic or holoendemic regions.

The chronic or repeated malarial infection produces hypergammaglobulinemia, normocytic normochromic anemia and splenomegaly. Production of cytotoxic IgM antibodies to suppressor (CD8+) lymphocytes leads to uninhibited B-cell production of IgM and formation of cryoglobulin (IgM aggregates and immune complexes). This immunological process stimulates reticuloendothelial hyperplasia and eventually produces splenomegaly.

Pathology

- In one variety, liver biopsy shows varying degree of sinusoidal lymphocytosis.
- In the second, liver histology is that of noncirrhotic portal fibrosis. Splenovenography reveals large dilated portal vein, and the intrasplenic pressure is increased.
- The third variety shows a combination of the pathologic features of both the varieties in liver biopsy.

Clinical Features

- Abdominal lump—splenic lump is usually of massive size (Fig. 21.4) but may be of just moderate size in some cases
- Abdominal pain suggesting perisplenitis
- Some hepatomegaly
- Anemia and some degree of pancytopenia
- Susceptibility to respiratory and skin infection.

Diagnosis

Diagnosis is by and large clinical. In majority of patients malarial parasites are not detectable in peripheral smear. However, fluorescent antibody titer against malaria is raised in many cases.



Fig. 21.4: Tropical splenomegaly. Note massive splenomegaly in an 8-year-old boy with chronic anemia and undernutrition.

386 Complications

- Portal hypertension
- Hypersplenism
- Malignant lymphoproliferative disorder as a result of clonal lymphoproliferation.

Treatment

Since etiology is far from clear, management is nonspecific.

- According to one school of thought, a prolonged course of antimalarial drugs (say chloroquine, one or two tablets every week for several months) is justified in all cases of tropical splenomegaly. Our experience in north Indian children indicates that such a regimen indeed leads to gratifying results in a significant proportion of cases. This observation also lends support to the current speculation regarding its etiology (vide above).
- A shunt operation and/or splenectomy benefits the group of patients with:
 - Advanced portal hypertension
 - Massive enlargement of spleen, causing severe and persistent abdominal pain and hypersplenism.

Prophylaxis

Antimalarial prophylaxis is recommended in children living in endemic areas.

LEISHMANIASIS

Leishmaniasis is defined as the spectrum of three illnesses that occur following the bite of female sandfly which transmits parasites belonging to the genus, *Leishmania*:

1. Visceral leishmaniasis (kala-azar)
2. Cutaneous leishmaniasis
3. Mucocutaneous leishmaniasis

KALA-AZAR (BLACK-SICKNESS*, VISCERAL LEISHMANIASIS)

Kala-azar is a chronic febrile illness of protozoal etiology, characterized by irregular fever, hepatosplenomegaly, malnutrition and anemia.

Etiopathogenesis

The etiologic agent is a protozoal parasite, *Leishmania donovani*. Transmission occurs by the bite of sandfly (Fig. 21.5). Parasitization of the reticuloendothelial system accounts for the salient features of the disease. Clinically manifest disease occurs when the protective immune response (predominantly cell-mediated immunity) breaks down as a consequence of factors such as malnutrition or human immunodeficiency virus (HIV) infection.

Subjects with HIV are particularly vulnerable to visceral leishmaniasis. In kala-azar-HIV coinfection, manifestations of leishmaniasis may not be typical.

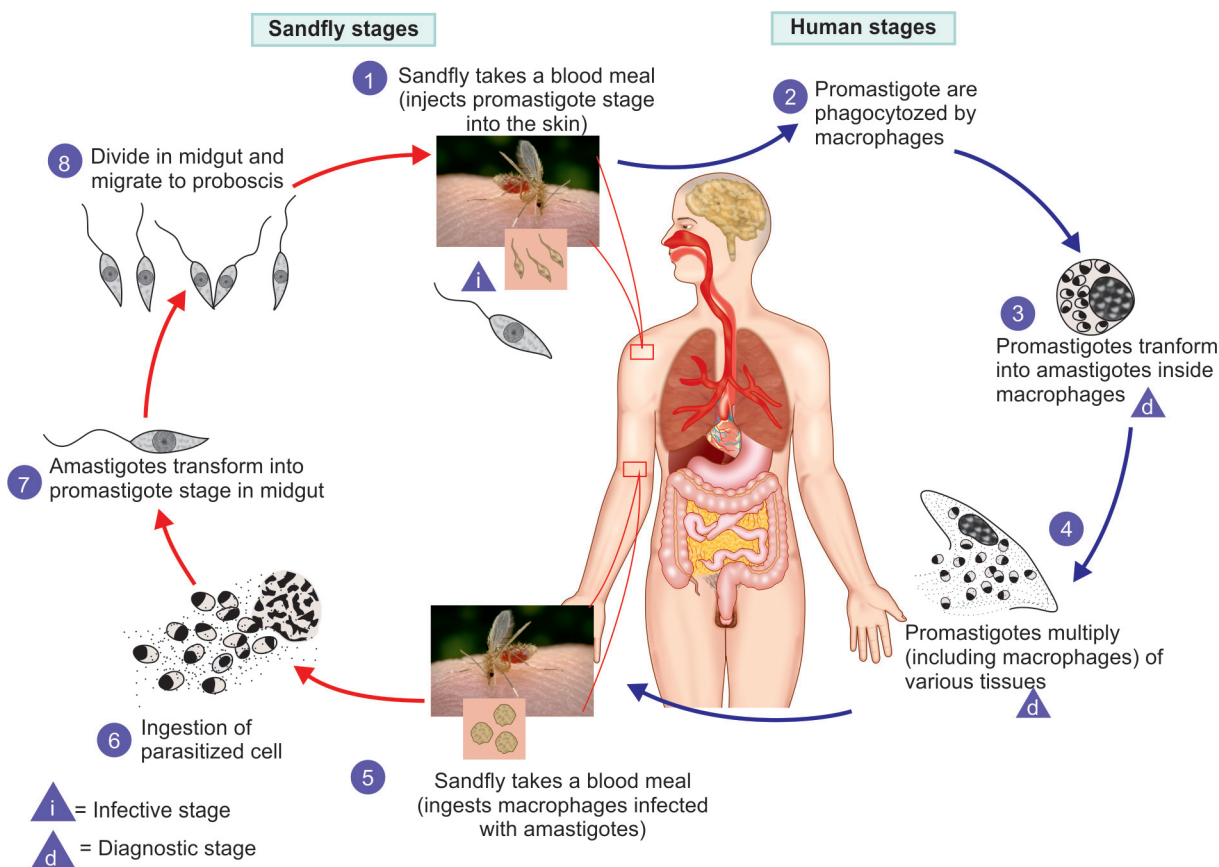


Fig. 21.5: Life cycle of *Leishmania donovani*.

*So termed because of the characteristic gray pigmentation of the skin seen in patients suffering from kala-azar.

Epidemiology

Kala-azar is widely distributed in certain parts of the World. In India, it is endemic in Sikkim, Assam, Bengal, Bihar, Orissa, Tamil Nadu, Karnataka, coastline bordering the Bay of Bengal and some parts of Uttar Pradesh and Madhya Pradesh.

The disease is more or less confined to rural areas, especially those along rivers and lakes. Its epidemics are known to follow famine and war. In recent years, kala-azar has shown a remarkable resurgence. In Bihar alone, the 1970 figure of 50,000 has shot up to approximately 300,000. Moreover, it no longer remains restricted to its known geographical belt, thereby altering its epidemiological scenario.

Clinical Features

Incubation period is 3–8 months with wide variations between 2 weeks and 3 years. Most vulnerable age group is 1–4 years though no age is a bar.

Three modes of onset of kala-azar are—(1) insidious (2) typhoid-like (3) malaria-like. A large majority of the cases have insidious onset. Clinical picture in the older children and infants differs considerably. Thus, two types are generally described: childhood type and infantile type.

1. **Childhood type:** It is seen in older children and resembles the adult type. Persistent, mild to moderate pyrexia with rapid enlargement of spleen in 2 weeks, time is the characteristic feature; liver enlargement occurs rather slowly (Fig. 21.6). Malnutrition (with considerable weight loss) in association with pigmentation of skin and sparse, falling and brittle hair are the additional manifestations. Appetite is, however, good.
2. **Infantile type:** Here, the onset is acute with high fever, rigors and vomiting. Lymphadenopathy and slight anasarca may be present. It is nearly always fatal.

Atypical clinical features of kala-azar in leishmania-HIV coinfection are in relation to upper airway or gastrointestinal tract. Hepatosplenomegaly may be conspicuous by its absence.

Complications

The following serious complications may occur in kala-azar.

- Pneumonia
- Dysentery



Fig. 21.6: Kala-azar. Note the hepatosplenomegaly. The presentation was with prolonged pyrexia of several months duration.



Fig. 21.7: Cancrum oris (gangrenous stomatitis, noma). Note the gangrene of the buccal mucosa resulting in a perforating ulcer of the cheek in the child suffering from kala-azar. Invasion by anaerobic microorganisms is the cause.

- Cancrum oris—also called **gangrenous stomatitis**, it is characterized by gangrene of the cheek (Fig. 21.7) and adjacent structures and is believed to be caused by an organism of the *Treponema vincentii* type. This particular organism is capable of producing rapid tissue destruction in a debilitated patient
- Severe hemorrhage
- Agranulocytosis
- Jaundice
- Stomatitis
- Gingivitis.

Differential Diagnosis

Differentials include tropical splenomegaly, chronic malaria, brucellosis, Hodgkin disease, leukemia, tuberculosis, Banti spleen and hemolytic anemias. At times, cirrhosis and storage diseases also warrant exclusion.

When the onset is typhoid-like, kala-azar should be differentiated from enteric fever, septicemia, miliary tuberculosis, brucellosis and hepatic amebiasis. Kala-azar with malaria-like onset needs differentiation from malaria, UTI, tuberculosis, etc.

Diagnosis

Clinical suspicion of kala-azar needs laboratory confirmation. Diagnosis is substantiated by direct demonstration of amastigote form of parasites (Fig. 21.8) in bone marrow, spleen, liver and lymph node aspirates or promastigote forms in culture of aspirated materials.

- Splenic aspiration and smear examination is the most sensitive (95%), but prior assessment of coagulation profile including platelet count and international normalized ratio (INR) are essential as this procedure may lead to hemorrhage in and around spleen

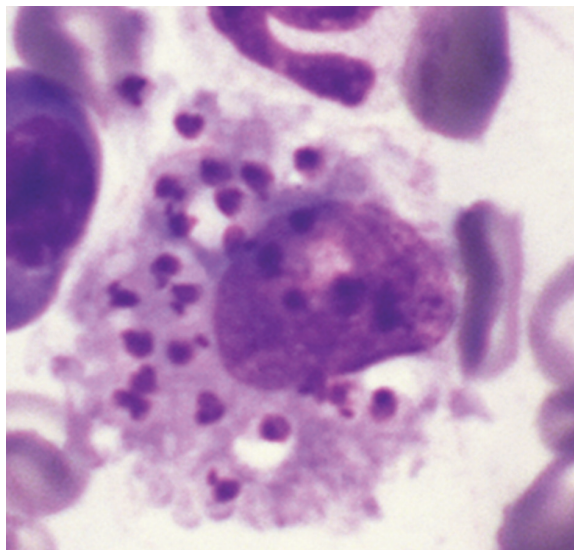


Fig. 21.8: *Leishmania donovani*.

and if massive may lead to death in children. The contraindication of splenic aspiration is INR more than 2.5 and platelet count less than 40,000/cu mm.

- Bone marrow aspiration is easy to do and without any risk and is positive in 60–80% of cases. Lymph node aspiration and liver biopsy are positive in 60% and 50% of cases respectively.
- Peripheral smear in kala-azar usually shows anemia, thrombocytopenia, neutropenia and lymphocytosis. Eosinophils are usually absent. The ratio of white blood cells (WBC) to RBC may be altered from 1:750 to 1:2,000–1:10,000.
- Serological tests:
 - **Aldehyde test (Napier test)** is a very simple and nonspecific test for kala-azar. The sensitivity of test is 35–94% with poor specificity. False-positive reactions may occur in children with cirrhosis, malaria and multiple myeloma. The increase in immunoglobulin is the basis of this test. In this test, one or two drops of formalin (40%) are added to 1–2 mL of patient's serum in a test tube. The egg white jellyfication of serum with opacification within 2–20 minutes indicates strongly positive reaction and within 24 hours, weakly positive.
 - Others serological tests with their sensitivity and specificity are outlined in Table 21.2.

Serological tests are indirect evidence of kala-azar. Direct agglutination test is very useful in diagnosis and epidemiological studies whereas enzyme linked immunosorbent assay (ELISA) is useful to follow the disease during and after therapy. Recently, dip-stick ELISA and *Leishmania* antigen and antibody detection in urine have been found to be of value.

- **Polymerase chain reaction:** The discovery of minicircle sequence of kDNA is unique and species specific. PCR offers the best approach to parasite detection and characterization by amplifying sequence found in minicircle of *Leishmania* using two primers—**LSUC** and **LSUL**. The test is 100% sensitive and specific and can detect a single parasite in biological sample.

Table 21.2: Serological tests (other than aldehyde test) with their sensitivity and specificity in diagnosis of kala-azar

Serological tests	Sensitivity	Specificity
Complement fixation test (1:8)	96%	—
Counter immunoelectrophoresis	80–100%	—
Indirect fluorescent antibody test (1:28)	100%	98%
ELISA	98%	100%
DAT (1:1600)	100%	100%
FML	99%	100%

Abbreviations: ELISA, enzyme linked immunosorbent assay; FML, fucose-mannose ligand; DAT, direct agglutination test.

Treatment

The specific treatment consists of administration of anti-leishmanial drug(s). In last decade, a lot of new parenteral drugs have been tried and found to be effective but availability of oral antileishmanial drug has revolutionized therapy.

Pentavalent antimonials, sodium stibogluconate (SSG), meglumine antimonite and urea stibamine are still the drug of choice for treatment of kala-azar despite a gradual increase in resistance against it. WHO has recommended that SSG should be used in a dose of 20 mg/kg/day (Maximum 850 mg) IM once daily for 30 days but duration may be extended up to 40 days in nonresponders. 60–80% of injected drug undergoes renal excretion within 6 hours, therefore toxicities are very low. Children tolerate this drug better than adults. Toxic effects of SSG are hypersensitivity, arthralgia, myalgia, hepatitis, renal dysfunction, myocarditis and rarely pancreatitis (Table 21.3).

- **Pentamidine isothionate** is recommended in patients resistant to antimonials and cases associated with tuberculosis. The dose is 3–5 (4) mg/kg IV slowly daily or alternate day for a total of 10–15 doses. The drug should be given usually with 10% or 25% dextrose to avoid hypoglycemia. The efficacy of this drug is 77–81.5%. Toxic effects are hypo- or hyperglycemia, hypotension, tachycardia, nephrotoxicity, gastrointestinal disturbances, arrhythmias and sudden death. It should be given in a supervised setting because of danger of hypersensitivity reaction.
- **Amphotericin-B**, an antifungal antibiotic which acts by binding to and inhibiting synthesis of sterol in the membrane of parasites creating multiple holes is very effective in resistant and relapse of kala-azar. The dose is 0.5–1 mg/kg IV with 5% dextrose over 6 hours daily or alternate day till a cumulative dose of 7.5–20 mg/kg. Toxic effects are anaphylaxis, thrombocytopenia, convulsions, chills, fever, thrombophlebitis, anemia, hypokalemia, nephrotoxicity, liver and cardiac damage. So, all patients should be continuously monitored clinically and for electrolyte disturbances particularly hypokalemia. Recently liposomal amphotericin-B has been found to be very effective in multidrug resistant kala-azar. The dose is 2 mg/kg IV alternate day or weekly for three doses (cumulative dose—6 mg/kg body weight). The drug achieves a higher concentration in reticuloendothelial system with more targeted response and no appreciable toxicities.

- **Aminosidine** is an effective (95%) and well-tolerated antileishmanial drug. The dose is 12–15 mg/kg/day IM for 21 days. Some authors recommend this drug as first-line antileishmanial drug in endemic areas of kala-azar. It may be used in combination with SSG to achieve high cure rate.
- **Miltefosine**, a phosphocholine analog, which was developed as antimalignant drug has shown to be highly active against *Leishmania donovani* and achieved 97% cure in phase 3 trial in India. It is given orally in a dose of 2.5 mg/kg/day OD or BD for 28 days. Side effects are transient and reversible and include gastrointestinal disturbances, hepatic and renal dysfunction. It is cheap, safe, very effective and easy to administer. The availability of miltefosine would benefit even in rural areas and could serve as control measures. The drug should not be given in children below 2 years of age.
- **Interferon- γ** , 100 $\mu\text{g}/\text{m}^2$ body surface/day subcutaneously (SC) for 30 days, is an immunochemotherapeutic alternative for cases with repeated failure of conventional therapy. It improves the immune response as well as reduces the dose of antimonials.
- **Other antileishmanial drugs** which can be used as adjunct are allopurinol (5–8 mg/kg PO for 1–3 week), metronidazole, methylbenzylesters of leucine, inosine analogues, primaquine, cotrimoxazole and rifampicin. Splenectomy needs to be reserved for cases with poor response to conventional antileishmanial drug and massive splenomegaly. It should be followed by SSG, 20 mg/kg/day IM for 20–40 days and penicillin prophylaxis. Prior to splenectomy, children must be vaccinated against *Meningococcus*, *Pneumococcus* and *H. influenzae*.

Monitoring of Therapy

Children on antileishmanial therapy should be monitored clinically (fever), hematologically (Hb%, total leucocyte count {TLC}, differential leukocyte count {DLC}), biochemically C-reactive proteins (CRP), and for splenic size and parasitological index. Patients are categorized as cured if fever disappears, anemia and leucopenia improves and parasitological index is zero at the end and 6 months of therapy.

Prophylaxis

The sheet-anchor of preventive attack is control of sandfly and early detection and treatment of kala-azar cases. Effective treatment of patients along with vector control has turned out to be a successful approach in controlling transmission. Kala-azar vaccine, based on a combination of *Leishmania* antigen and Bacillus Calmette Guerin (BCG) vaccine, is round the corner.

Prognosis

About 13–20% cases of kala-azar are said to have spontaneous cure. The remaining generally respond well to treatment, provided it is started not-too-late. In some, the response may, however, be slow. Emergence of drug resistance (both primary and secondary), somewhat related to delay in diagnosis and treatment, is a disturbing phenomenon. Recurrences are well known.

GIARDIASIS

Giardiasis, a cause of considerable morbidity and mortality in infancy and childhood, results, from infestation with the protozoal flagellate, *Giardia lamblia*. It is noteworthy that this protozoan was regarded as a commensal for a long time. In recent decades, considerable evidence has accumulated establishing its pathogenicity. This is quite a fascinating example of how medical concepts undergo radical changes.

Giardiasis is especially more common in subjects with malnutrition or immunodeficiency, say agammaglobulinemia or selective IgA deficiency, as also in day care centers and residential institutes for the mentally retarded.

Etiopathogenesis

Giardia lamblia infects through ingestion of cysts—person-to-person, water-borne, food-borne or interspecies transmission.

On arrival in the upper small intestine, each cyst liberates four trophozoites which colonize the lumen of the duodenum and the proximal jejunum. Here, they attach to the brush border of the intestinal epithelial cells and multiply by binary fission. Its powerful sucking disk on its ventral surface causes insult to the microvilli of the intestinal mucosa, resulting in deficiency of the enzymes, **disaccharidases**, in the enterocytes.

In addition, there may be pancreatic damage, causing extraintestinal steatorrhea and poor tryptic activity, deficiency of enterokinase secretion, fat malabsorption due to mechanical defect as well as overgrowth of bacteria in the duodenum and upper jejunum and deconjugation of bile salts, liberating free bile acids. IgA (secretory) in duodenal aspirate is low. T cell function is depressed.

Clinical Features

Incubation period (following ingestion of cysts) is 7–14 days. Symptomatic patients have vague upper abdominal pain, recurrent diarrhea (stools are generally steatorrheic and often whitish), poor appetite (at times appetite may be voracious), failure to thrive and nutritional deficiencies. Occasionally, there may be acute dysentery-like presentation. Even transient ulcerative colitis-like presentation has been described.

Diagnosis

- Stool microscopy—since *Giardia lamblia* cysts are passed intermittently in stools, several stool samples (at least 3, preferably 6) on successive or alternate days are needed for meticulous microscopy. Yet, 25–50% infected subjects may be missed (Fig. 21.9).
- **Direct fluorescent antibody test** and enzyme immunoassay for *Giardia lamblia* antigen in stools is more sensitive than stool microscopy.
- A duodenal aspirate (or peroral/endoscopic biopsy) is a better method of detecting *Giardia lamblia*. It is called **Enterotest**.
- Endoscopic brush cytology is a yet superior diagnostic tool.



Fig. 21.9: *Giardia lamblia*. Note the trophozoite form of *Giardia lamblia*.

- ELISA promises to be an inexpensive, efficient and simple method for detecting *Giardia lamblia* in stool sample rapidly.

Pharmacotherapy

- **Mepacrine** (Atabrine), 5–8 mg/kg/day (divided doses) for 5–7 days gives excellent clinical as well as parasitologic cure of the magnitude of nearly 100%. Unfortunately, it has very bitter taste, is poorly tolerated and is toxic. Transient yellow staining of the skin may occur in some patients. Moreover, it is not easily available now. These considerations limit its routine use in the therapy of this infestation. The following drugs have replaced it:
- **Metronidazole** comes fairly close to mepacrine in efficacy. Today, it occupies pride in the place as an anti-giardia agent. It is quite safe. Since it is excreted in the saliva, a bad taste in the mouth is often irritating to the patient. The dose is 10–20 mg/kg/day for 5–7 days. The drug is best given in divided doses. Remember, subjects on phenobarbital therapy should receive 2–3 times higher dose of metronidazole to be effective.
- **Tinidazole** is remarkably effective as an anti-giardial agent. Given in a dose of 50 mg/kg once only, it yields a high clinical and parasitologic cure rate. Tinidazole may also be administered in a dose of 20 mg/kg/day for 5 days. It is fairly safe.
- **Secnidazole**, in a dose of 30 mg/kg, once only, too yields a high cure rate. It is quite safe.
- **Furazolidone** is another potent anti-giardial drug. It is administered in a dose of 8 mg/kg/day (divided doses) over a period of 10 days. It may cause some gastrointestinal upset and headache. It invariably stains the urine. Occasionally, mild drug rash may occur.
- **Albendazole**, 400 mg (200 mg for <2 years) daily for 5 days also gives gratifying results.
- **Ornidazole**, a relatively new imidazole, 40 mg/kg as a single dose once only, is not only very effective, but is better tolerated by children compared to the earlier imidazoles. Nitazoxanide, 7–10 mg/kg/dose twice daily for 3 days, gives excellent results. Side-effects include abdominal pain, diarrhea, vomiting and headache.

It is also effective against *Cryptosporidium parvum*, *Entamoeba histolytica* and helminthes. Fascioliasis needs treatment for 7 days.

- **Nitazoxanide**, 7–10 mg/kg/dose given twice a day for 3 days, yields excellent outcome. Alternative dosage regimen is 1–4 years—100 mg BID; 4–12 years—200 mg BID; above 12 years—500 mg BID.

Resistant/Repeated Giardiasis

Not infrequently, children with resistant symptomatic giardiasis need repeated courses of an anti-giardial agent as such or in different combinations. The probability of hypogammaglobulinemia must be considered in children who fail to respond to repeated courses of such a therapy. The so-called **resistance** needs to be differentiated from a common situation in which repeated infection occurs as a result of continuing exposure to poor food and water hygiene and environmental sanitation which indeed affects most members of the family or the institution.

AMEBIASIS

Infection with the protozoa, *Entamoeba histolytica*, is relatively less common in infancy and childhood. The incidence is far less than the average of 20% seen in our adult population.

Etiopathogenesis

Infection is transmitted by contaminated water and food either through food handlers or direct contact with infected stools.

On arrival in the small intestine, the trophozoites of *Entamoeba histolytica* float in the intestinal contents. On reaching the large intestine, they invade the intestinal mucosa, causing tissue destruction in the form of ulcers with slight inflammatory response. The cecum, transverse colon and the rectosigmoid region are most vulnerable to insult because of slow movement of the colonic contents.

E. histolytica may reach the liver through blood stream and produce similar lytic lesions, the so-called **amebic liver abscess**. The abscess is usually sterile, containing viscid, chocolate-colored nonpyogenic material. It may be single or multiple. Amebic empyema and pulmonary amebiasis may result following transdiaphragmatic rupture of liver abscess.

Occasionally, *E. histolytica* may disseminate to lungs or brain through hematogenous spread. Rarely, amebae may enter the brain through olfactory neuroendothelium in swimmers. These free living amebae (*Naegleria* or *Hartmannella Acanthamoeba* group) cause a new form of meningoencephalitis.

Clinical Features

Incubation period is long, ranging from weeks to months. The symptoms range from mild gastrointestinal upset to acute dysentery/diarrhea or chronic colitis. Unlike adults who may have only loose motions, children usually pass mucus (free of pus) together with blood. The latter is generally not mixed with the fecal matter or the mucus. Abdominal pain and tenesmus may also accompany.

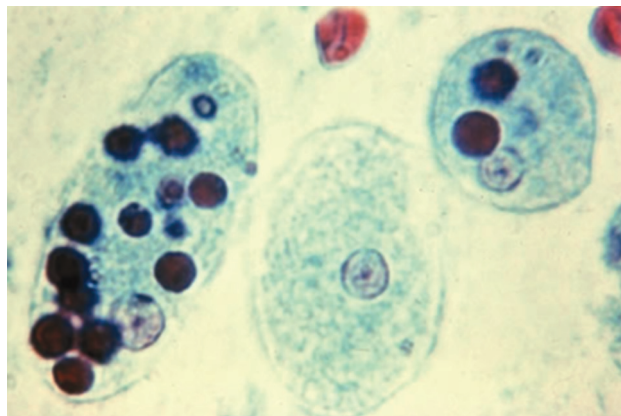


Fig. 21.10: *Entamoeba histolytica*. Note the trophozoites with ingested erythrocytes.

Complications include amebic liver abscess, hepatitis, partial or complete intestinal obstruction, intussusception, perforation of the colon, peritonitis and rectal ulcers and fistula. Rarely, empyema may occur. A group of patients may remain symptom-free though they pass cysts in their stools. The incidence of symptom-free cyst-passers in pediatric practice is very low.

Diagnosis

Diagnosis is based on demonstration of *E. histolytica* cysts or trophozoites in stool samples. At least three and preferably six samples need to be meticulously examined microscopically on successive days to rule out amebic infection of the gut. Alternatively, smear of the ulcerated area of the rectal mucosa may be examined microscopically for the organisms. Demonstration of ingested erythrocytes within trophozoites is said to be pathognomonic of the infestation (Fig. 21.10).

In case of liver abscess, aspirates should be examined for *E. histolytica*. In highly suspected subjects in whom stool samples continue to be negative, endoscopy and biopsies should be performed. Serology (indirect hemagglutination {IHA} test, ELISA, etc.) may assist in diagnosing invasive intestinal infection and amebic liver abscess. A titer of at least 1:128 in IHA is diagnostic.

In suspected amebic liver abscess, additional investigations such as chest X-ray (CXR), ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), isotope scan, etc. may be warranted for localizing the abscess.

Pharmacotherapy

Amebic Colitis

Metronidazole, 20–50 mg/kg/day, for 10–14 days, gives excellent results. A high daily dose rather than the prolonged duration of therapy is important. Along with metronidazole, a suitable luminal amebicide—diiodohydroxyquin (iodoquinol) or, still better, diloxanide furoate which is safer and yet more effective than the former, or paromomycin should be given for eradication of cysts. This should be given following metronidazole therapy.

Alternatively, especially if the illness is severe or if metronidazole cannot be employed for some reason, dehydroemetine, 1 mg/kg/day (IM or SC) for 10 days, is

Box 21.5

Indications for needle aspiration of amebic liver abscess

- Failure of manifestations to respond to adequate drug therapy
- Massive abscess, causing markedly elevated diaphragm
- Palpable abscess with impending rupture
- Persistent pain and tenderness locally with referred shoulder pain.

recommended. In view of possibility of cardiac or renal complications, dehydroemetine must be administered in the hospitalized patient only. Therapy with this drug must be followed by a course of diloxanide furoate.

Amebic Liver Abscess

Metronidazole is effective in hepatic involvement as well. Excellent result has been obtained in amebic liver abscess with IV metronidazole, 21 mg/kg/day in 3 divided doses as infusion, followed by oral medication for 10 days. Dehydroemetine is also very effective. Some prefer to use chloroquine hydrochloride, along or in combination with another antiamebic drug. Liver abscess may require needle aspiration in addition to drug therapy in certain situations (Box 21.5).

- **Tinidazole** in a dose of 50–60 mg/kg/day for 3 days gives excellent results.
- **Secnidazole**, in a dose of 30 mg/kg, given just once, too gives good results.
- **Ornidazole**, a relatively new imidazole, 40 mg/kg as a single dose once only, is not only very effective, but is better tolerated by children compared to the earlier imidazoles.
- **Nitazoxanide**, 7–10 mg/kg/dose given twice a day for 3 days, yields excellent outcome. Alternative dosage regimen is 1–4 years—100 mg BID; 4–12 years—200 mg BID; above 12 years—500 mg BID. ADRs include abdominal pain, diarrhea, vomiting and headache. It is also effective against *Cryptosporidium parvum*, *Entamoeba histolytica* and certain helminths. Fascioliasis needs treatment for 7 days.

FREE LIVING AMOEBAE

Free living amoebas are distinct from other pathogenic protozoa by:

- The nature of their free living existence
- The lack of an insect vector or human carrier state
- The limited relationship of poor sanitation with the spread of infection.

Two classes are recognized:

1. ***Acanthamoebae*** (amoeba of *Naegleria* and *Balamuthia* genera) causes two distinct clinical syndromes:
 - Keratitis in contact lens wearers who swim in fresh water. It may be complicated by cataracts, hypopyon and increased intraocular pressure
 - Granulomatous amoebic encephalitis (GAE) which occurs in patients with underlying disease, such as HIV/AIDS (with CD4 count <200 cells/ μ L), liver disease, organ transplantation, and diabetes mellitus. GAE has a very high mortality rate.

- 392 2. *Naegleria fowleri* which causes primary amoebic meningoencephalitis.

Diagnosis

- Diagnosis is usually made by demonstration of cyst in corneal scrapings after staining with calcofluor white and examination under fluorescent microscopy.
- PCR is useful to identify organisms.
- In children with neurological manifestations, cerebrospinal fluid examination reveals an increased number of white blood cells (as many as 800 cells/mm³, primarily lymphocytes), elevated protein and decreased glucose.
- CT scan of brain shows multiple nonenhancing lesions in cortex and ventriculomegaly.

Treatment

- Acanthamoebae
 - Treatment for keratitis is topical. Two types of preparations are recommended: diamides (propamide isethionate and hexamide) and cationic antiseptics (polyhexamethyl biguanide and chlorhexidine)
 - Ketoconazole, sulfamethazine or pentamidine, cotrimoxazole and flucytosine should be used for GAE. Mortality is very high.
 - Chlorhexidine gluconate and ketoconazole cream are very effective in skin lesions.
- *Naegleria fowleri*
Primary amoebic meningoencephalitis, despite treatment with amphotericin B in high doses (IV, intrathecal [IT]), chloramphenicol and rifampicin has very high mortality.

TOXOPLASMOSIS

It is the result of infection by protozoan, *Toxoplasma gondii*. The most common source of infection is the infected cat (from eating contaminated meat) that excretes oocytes in feces.

The pregnant women acquire infection during pregnancy, except immunocompromised ones who may be already chronically infected. Usually, maternal infection is asymptomatic except for lymphadenopathy.

Most perinatal infections occur in the last trimester or labor (transplacentally or during vaginal delivery), causing only minor manifestations in the infant. Only about 17% of *in utero* infections occur in first trimester, causing serious insult to the fetus including abortion, death, hydrops fetalis, intrauterine growth restriction (IUGR),

prematurity, and the well-known triad of “hydrocephalus, chorioretinitis and cerebral calcifications”.

For more details on congenital toxoplasmosis, See Chapter 23 (Intrauterine Infections). Ocular toxoplasmosis occurs in case of reactivation of the infection in an asymptomatic patient.

CRYPTOSPORIDIOSIS

The intestinal protozoan, *Cryptosporidium*, is now recognized as an important cause of self-limited acute watery diarrhea in immunocompetent subjects and protracted watery diarrhea in immunocompromised patients such as having acquired immunodeficiency, e.g. HIV/AIDS, or congenital immunodeficiency.

Etiopathogenesis

Infection is transmitted by feco-oral route, person to person, through water and food. After the oocytes are established in the gut, excystation occurs. Further development occurs at the surface of the intestinal epithelium. Jejunum is the usual seat of *cryptosporidium*. In immunocompromised individuals, it may invade the colon and the biliary tract. In such patients, it may cause cholecystitis, pancreatitis and papillary stenosis. Even in children who are immunocompetent, cryptosporidiosis should be considered as an important factor in development of malnutrition.

Clinical Features

Incubation period is 2–7 days. Manifestations in immunocompetent children include acute watery diarrhea, vomiting and abdominal cramps. Infection subsides in 10–14 days on its own. In immunocompromised children, manifestations include severe watery diarrhea which tends to become persistent, resulting in weight loss and malnutrition.

Diagnosis

Laboratory detection of the cases is difficult. Identification of the oocytes is by special acid-fast staining method on stool sample or mucosal biopsy specimen.

Treatment

Immunocompetent children with diarrhea from cryptosporidiosis need no specific therapy except for fluids and electrolytes and adequate nutrition. In immunodeficient children, protracted diarrhea is not responsive to any drug therapy. In reversible immunodeficiency, elimination of immunosuppression leads to recovery.

Multiple Choice Questions

1. Factors contributing to false-negative blood film in highly suspected malaria include each of the following, except:
 - A. Failure to examine a minimum of 100 fields and at least 3 smears at 6–8 hour gap
 - B. Coexisting *P. vivax* and *P. falciparum*
 - C. Immunocompromised state
 - D. Massive parasitemia causing sequestration

contd...

2. All of the following observations about kala-azar are true, except:
 - A. Parasitization (by *Leishmania donovani*) of the reticuloendothelium system accounts for the clinical features
 - B. In kala-azar-HIV coinfection, manifestations of leishmaniasis may not be typical
 - C. Splenic aspiration and smear examination is the most sensitive (95%) diagnostic test
 - D. Around 50% cases of kala-azar may undergo spontaneous cure
3. Spot the wrong observation about *Giardia lamblia*:
 - A. Entero-test is by and large the best and most dependable tool for detecting it
 - B. Infestation with this protozoa usually causes anorexia
 - C. Ivermectin is effective in its therapy
 - D. It may cause insult to the microvilli, resulting in disaccharidase deficiency and lactose malabsorption
4. Spot the wrong observation about *Entamoeba histolytica*:
 - A. Frequency of occurrence is more in children than adults
 - B. The incidence of symptom-free cyst-passers in pediatric practice is very low
 - C. Metronidazole is effective in intestinal as well as hepatic involvement
 - D. Tinidazole in a dose of 50–60 mg/kg/day for 3 days gives excellent results

Answers

1. B 2. D 3. C 4. A

Clinical Problem-solving

Review 1

A boy, aged 6 years, is admitted with 4 days' history of paroxysms of high fever with chills and rigors, headache, irritability, lethargy, moderate anemia and hepatosplenomegaly. Meningeal signs are absent. Blood film (done in a private laboratory) is positive for both *P. vivax* and *P. falciparum*. As he is being managed, he develops generalized tonic-clonic seizures. In the subsequent an hour or so his sensorium progresses to coma.

1. What is the most likely diagnosis?
2. Are you serious about this diagnosis in spite of the fact that there are no meningeal signs?
3. How do you explain coinfection with both *P. vivax* and *P. falciparum*?
4. What is the major approach to treatment?

Review 2

An HIV-positive infant, aged 5 months, is being exclusively breastfed by the HIV-positive mother. Both are on appropriate antiretroviral therapy (ART). The infant develops watery diarrhea with moderate dehydration which persists for more than 2 weeks causing malnutrition.

1. What is the most likely cause of diarrhea?
2. What is its treatment?
3. Does this protozoa cause any complications other than watery diarrhea, dehydration and malnutrition?

Answers

Review 1

1. Severe/complicated malaria, in all probability cerebral malaria.
2. Yes, it is well known that in cerebral malaria, meningeal signs are usually absent.
3. In holoendemic and hyperendemic regions where both species are prevalent, it is not unusual to find cases with blood smears positive for both *P. vivax* and *P. falciparum*.
4. Treatment of complicated (severe) malaria, no matter it is vivax or falciparum, is on the same lines, invariably employing parenteral therapy. In the present case we need to employ the parenteral artemisinin-based regimen. Alternatively, quinine IV infusion may also be used.

Review 2

1. The intestinal protozoan, *Cryptosporidium*, is the most likely cause of superimposed diarrhea in this patient. It is now recognized as an important cause of protracted watery diarrhea in immunocompromised patients such as having HIV/ AIDS or congenital immunodeficiency.
2. Treatment is purely symptomatic, targeting correction of dehydration and improvement in nutritional status. No drug is effective against this protozoa.
3. Complications of cryptosporidiosis in immunocompromised children include cholecystitis, pancreatitis and papillary stenosis.

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2. Gupte N, Gupte S, Jan A. Pharmacotherapy of pediatric malaria. In: Gupte S, Gupte SB, Gupte M (eds): *Recent Advances in Pediatrics-21: Hot Topics*. New Delhi: Jaypee 2013:478–90.
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4. Piscope TV, Azzopardi CM. Leishmaniasis. *Postgr Med J* 2006;82:649–57.
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BOOK/MONOGRAPH

1. World Health Organization. *Burden of Protozoal and Helminthic Infestation*. Geneva: WHO 2010.

CLASSIFICATION

Helminthes are parasitic worms which thrive at the expense of the host. Human helminthes are of three types:

- **Nematodes (roundworms)**
 - **Gut-related:** *Ascaris lumbricoides*, *Enterobius vermicularis*, *Ancylostoma duodenale*, *Necator americanus*.
 - **Extragut-related:** *Microfilariae*, *LoaLoa*, *Onchocerca volvulus*, *Trichinella spiralis*, *Dracunculus medinensis*, *Toxocara canis*, *Strongyloides stercoralis*, *Trichuris trichiura*.
- **Cestodes (tapeworms):** *Taenia solium*, *Taenia saginata*, *Hymenolepis nana* (dwarf tapeworm), *diphyllobothrium latum*.
- **Trematodes (flukes):** *Schistosoma* (blood-flukes)—*spp. hematobium*, *mansoni*, *japonicum*.
- **Liver flukes**—*Fasciola hepatica*; **Lung flukes**—*Paragonimus westermani*; **Intestine flukes**—*Fasciolopsis buski*.

ASCARIASIS

(*Ascaris lumbricoides* Infestation)

The great roundworm, *Ascaris lumbricoides*, perhaps accounts for the highest proportion of intestinal parasitosis, nay for the most common worm infestation of humans. Almost 25% of the world population is supposed to have this infestation, though a majority of them may be **symptom-free** because of low worm load.

Ascaris lumbricoides is about 10–20 cm in length and creamy in color (Fig. 22.1). Its appearance is so characteristic that the diagnosis is practically beyond doubt when there is history of passage of snake-like worms in the stools or in the vomitus. Often, these worms scare the young child.

Etiopathogenesis

The larva-containing egg (oval, $40 \times 60 \mu\text{m}$) passed in the stools of infected individuals is the infective stage of *A. lumbricoides*. This egg matures in 5–10 days to become infective under favorable conditions. When the mature egg is swallowed by the human host, it hatches out in the duodenum to release larvae which penetrate the intestinal wall, enter the venous circulation and migrate to the lungs. From the alveolar spaces, larvae ascend the bronchial tree and the trachea, cross over the epiglottis, and are re-swallowed to reach the small intestine where they mature

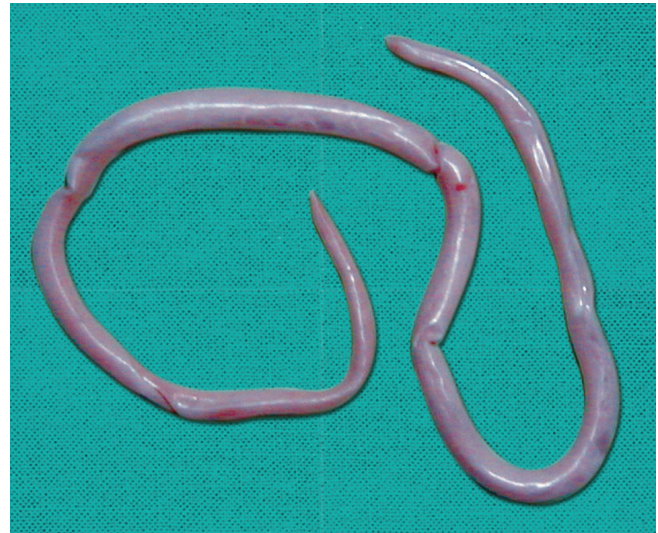


Fig. 22.1: *Ascaris lumbricoides*. Note the snake-like adult worm. It may measure 10–20 cm to as much as 40 cm.

into adult worms. Each female roundworm is capable of producing 200,000 eggs a day and surviving for 1–2 years.

Clinical Features

Clinical picture depends on the worm load, child's nutritional status and worm location in or outside the gastrointestinal tract (GIT).

- **Intestinal ascariasis:** Abdominal discomfort, pain and/or distention, vomiting, growth failure, anemia, vitamin deficiencies and voracious appetite. Pica, sleeplessness, irritability, urticaria, eosinophilia and diarrhea are associated in some cases. Occasionally, worms may cause intestinal obstruction, cholecystitis/cholangitis, liver abscess and pancreatitis. Small intestinal function and structure, however, remain normal.
- **Pulmonary ascariasis:** Migration of larvae may cause ascaris pneumonia (Loeffler syndrome) with fever, cough, breathlessness; asthma-like manifestations (wheeze, gross eosinophilia and leucocytosis); and lung infiltrates.
- **Other manifestations:** Urticaria, hepatomegaly, splenomegaly, encephalopathy; retinoblastoma-like picture from involvement of the eye.

Diagnosis

It is based on:

- Observation of adult worms in vomitus or stools



Fig. 22.2: *Ascaris lumbricoides*. Note the microscopic appearance of fertilized egg.

- Identification of ova (eggs) in stool samples on microscopy (Fig. 22.2)
- Imaging studies showing worms in GIT or pancreaticobiliary ducts.

Pharmacotherapy

Modern drugs employed in therapy of ascariasis include albendazole, mebendazole, nitazoxanide and ivermectin (Table 22.1). The use of the conventional piperazine is now limited to intestinal obstruction from massive worm load.

OXYURIASIS

(Enterobiasis, Pinworm Infestation, Threadworm)

Infestation with *Enterobius vermicularis*, popularly known as **threadworm** or **pinworm**, is very common, particularly in infants and young children. Often, there is a history of passage of worms, measuring 2–3 mm in length, which is invariably reliable. Routine stool examination usually misses the ova. Cellophane tape technique should be employed in doubtful cases.

Etiopathogenesis

Embryonated eggs carried under fingernails following perianal scratching, on clothing, bedding or house dust infect human host (the only natural host of *E. vermicularis*) after being ingested. Eggs hatch in the small intestine. The larvae migrate into cecal region where they mature into adult worms. The gravid female wanders by night to the perianal region to lay eggs, causing intense pruritus. Each egg measures 30–60 μm and matures after 6 hours into a single coiled larva which has a viability of 20 days.

Diagnosis

- Observations of the worms in stools or over perianal region.
- Demonstration of eggs (Fig. 22.3) in perianal swab obtained before the child has defecated.
- Cellophane technique—a transparent cellulose acetate strip is applied over the child's perianal region, then

lifted and pressed on a glass slide for microscopic examination.

Clinical Features

Pruritus ani, with or without superadded infection due to intense scratching is the most common manifestation. In some girls, there may be associated vulvovaginitis. Irritability, restlessness, sleep disturbances, behavior problems like grinding of teeth, masturbation, and enuresis, abdominal pain, diarrhea and poor appetite are present in a proportion of the cases. Rarely, threadworms may cause serious complications like appendicitis and salpingitis.

Treatment

- **Pharmacotherapy:** Currently, albendazole, mebendazole and pyrantel pamoate are the drugs of choice (Table 22.1).
- **Supportive measure:** Hand hygiene, cutting short of nails and treatment of other family members simultaneously is important.

ANCYLOSTOMIASIS

(Hookworm Infestation)

Hookworm infestation is particularly common among the rural population and the slum-dwellers of the towns.

Etiopathogenesis

Hookworm larvae, living in favorable environmental conditions (warm, damp soil), become infective in 1–2 weeks by molting twice and penetrate the human host's skin (usually bare foot). The larvae migrate to the venous circulation to reach the lungs. From the alveolar spaces, they climb upward and cross over the epiglottis when they are swallowed to reach the upper small intestine, their final habitat. In 2–4 weeks, they mature into adult worms, 5–13 mm in length. In next 6–9 weeks, they attain sexual maturity and start depositing eggs (*Ancylostoma duodenale* {30,000/day}, *Necator americanus* {9,000/day}) which are excreted in stools. Each egg measures 36 \times 58 μm and is characterized by four embryonic segments (Fig. 22.4). Larvae survive in the soil for 1–2 weeks before they turn infective. Hookworm infection may also be acquired by oral route.

Morbidity of hookworm infection depends mainly on the worm load and the diet of the host. Lesions may occur during the migratory phase (ground itch, mild pulmonary lesions) or presence of the adult worms in the small intestine (anemia as a result of 0.03–0.3 mL/worm/day blood oozing, hypoproteinemia).

Diagnosis

- Identification of the eggs in stool sample is by microscopy.
- Complete blood picture (CBP) for magnitude and type of anemia and presence of eosinophilia.

Table 22.1: Modern pharmacotherapy of helminthic infestations

Helminthic infestation	Drug(s)	Dosage	ADRs	Recommendatory remarks
Ascariasis	Albendazole	<ul style="list-style-type: none"> Less than 2 year: 200 mg once only 2 years: 400 mg once only 	GI upset, dizziness, rash, elevation of liver enzymes and reversible alopecia	Very effective; drug of choice
	Mebendazole	100 mg BID × 3 days	GI upset, rash and angio-edema	Very effective; drug of choice
	Ivermectin	150–200 µg/kg once only	Dryness of mouth, giddiness, headache, burning sensation, rash, palpitations, tremors and excessive sweating	Very effective; drug of choice
	Nitazoxanide	7–10 mg/kg BID × 3 days	GI upset, rash, headache, pruritus and chest pain	Effective; a good alternative
Ancylostomiasis	Albendazole	<ul style="list-style-type: none"> Less than 2 year: 200 mg once only 2 years: 400 mg once only 	See ascariasis	Very effective; drug of choice
	Mebendazole	100 mg BID × 3 days	See ascariasis	Very effective; drug of choice
	Pyrantel pamoate	11 mg/kg × 3 days	See ascariasis	Very effective; drug of choice
	Nitazoxanide	7–10 mg/kg BID × 3 days	See ascariasis	Effective; a good alternative drug
Enterobiasis	Albendazole	Less than 2 year: 200 mg once only 2 years: 400 mg once only	See ascariasis	Very effective; drug of choice
	Mebendazole	100 mg once only with a repeat dose after 1–2 weeks	See ascariasis	Very effective; drug of choice
	Pyrantel pamoate	11 mg/kg with a repeat dose after 1–2 weeks	See ancylostomiasis	Very effective; drug of choice
	Nitazoxanide	7–10 mg/kg q BID × 3 days	See ascariasis	Effective; a good alternative
Trichuriasis	Albendazole	As in ascariasis but for 3 days	See ascariasis	Effective; drug of choice
	Mebendazole	As in ascariasis but for 3 days		Effective; a good alternative drug
	Ivermectin	As in ascariasis but for 3 days		Effective; a good alternative drug
Strongyloidiasis	Ivermectin	See ascariasis	See ascariasis	Effective; drug of choice
	Albendazole	See ascariasis	See ascariasis	Effective; alternative drug
	Nitazoxanide	See ascariasis	See ascariasis	Effective; alternative drug
H. nana	Niclosamide	For weight 11–34 kg, initial dose is 1 g followed by 500 mg daily for 6 days. For over 34 kg weight, initial dose is 1.5 g followed by 1 g daily for 6 days. In terms of body weight dose is 40 mg/kg/day	GI upset, rash, headache, ataxia, paresthesia and sleep disturbances	Very effective; drug of choice
	Praziquantel	5–10 mg/kg/day as a single dose once only. In case of poor response, 15–25 mg/kg as a single dose	GI upset, malaise, headache, dizziness, urticaria, pruritus, low-grade fever	Very effective; drug of choice
T. saginata/T. solium	Niclosamide	See <i>H. nana</i>	See <i>H. nana</i>	Very effective; drug of choice
	Praziquantel	See <i>H. nana</i>	See <i>H. nana</i>	Very effective; drug of choice
Neurocysticercosis	Praziquantel	50–100 mg/kg/day × 7–28 days	See ascariasis	Very effective; drug of choice
	Albendazole (+steroids)	15 mg/kg/day in two divided doses × 7–28 days	See <i>H. nana</i> Steroid ADRs include hypertension, obesity, euphoria, cushingoid facies, acne, hyper-glycemia and pseudomotor cerebri	Very effective; drug of choice
Filariasis	Diethylcarbamazine	50 mg on day 1, 50 mg twice and thrice on days 2 and 3, respectively, then 10 mg/kg on days 4–21. Alternative regimen is 6 mg/kg/day in three divided doses for 12 days	Dizziness, headache, nausea, arthralgia, conjunctival congestion	Effective; drug of choice

contd...

Helminthic infestation	Drug(s)	Dosage	ADRs	Recommendatory remarks
	Albendazole	<ul style="list-style-type: none"> Less than 2 year: 200 mg once only More than 2 years: 400 mg once only 	See ascariasis. Antihistaminics ADRs include drowsiness, dryness of mouth, headache, etc.	Effective; alternative drug
Tropical eosinophilia	Diethylcarbamazine	6 mg/kg/day in three divided doses for 10–14 days	Filariasis	Effective; drug of choice
Hydatid cyst	Albendazole	15 mg/kg/day × 4–6 months with a fortnight interval between courses	GI upset, dizziness, rash, elevation of liver enzymes, reversible alopecia	Effective; drug of choice
Larva migrans (cutaneous)	Albendazole	<ul style="list-style-type: none"> Less than 2 year: 200 mg OD × 3 days 2 years: 400 mg OD × 3 days 	See ascariasis	Effective; drug of choice
	Ivermectin	200 mcg/kg OD × 2 days	See ascariasis	
Larva migrans (visceral)	Albendazole	<ul style="list-style-type: none"> Less than 2 year: 200 mg q 12 hourly × 5–20 days. 2 years: 400 mg q 12 hourly × 5–20 days 	See cysticercosis	Effective; drug of choice
	Mebendazole	100–200 mg q 12 hourly × 5–20 days	See ascariasis	Effective; drug of choice

Note: It is advisable to give a repeat course of the anthelmintic after 1–2 weeks, especially when infestation is heavy in most parasitosis.
Abbreviations: ADRs, adverse drug reactions; GI, gastrointestinal.



Fig. 22.3: *Enterobius vermicularis*. Note the appearance of an egg.

Clinical Features

The prominent clinical features are progressive anemia, anorexia, pain in abdomen and malnutrition. Pica is often present. Advanced cases may have gross anemia with hypoproteinemia, leading to edema and even anasarca. Diarrhea, alternating with constipation, may also be present. Some degree of malabsorption, as a result of histologic as well as functional damage to the small intestinal epithelium, occurs in many cases.

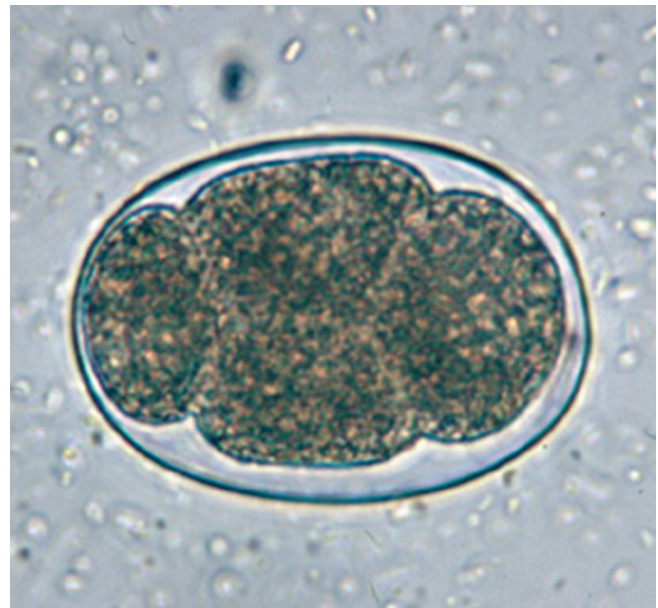


Fig. 22.4: Hookworm. Note the classical microscopic appearance of *Ancylostoma duodenale* egg.

The so-called **ground itch**, as a result of larval skin invasion over feet (buttock in infants), is often mild and unnoticed. Occasionally, it may be seen as an irritant, papulovesicular rash or even as cutaneous larva migrans.

Infantile hookworm disease is the term applied to a distinct clinical entity characterized by nausea, vomiting, restlessness, diarrhea with bloody stools, melena and anemia. Besides skin as the portal of entry, it can develop following transmammary transmission or, rarely even

transplacental transmission, if the mother is suffering from ancylostomiasis. Majority of its documentations are from China.

Treatment

- **Pharmacotherapy:** If hemoglobin is under 5 g/dL correction of anemia with iron and/or blood transfusion (packed cell) must precede rather than follow the anthelmintic therapy. Currently, albendazole, mebendazole and pyrantel pamoate are the recommended drugs against hookworm infestation (Table 22.1).
- **Supportive measures:** Discouraging bare-foot walking in soil.

STRONGYLOIDIASIS

Strongyloides stercoralis infection is not a common problem in our country. It resembles hookworm in many ways.

Etiopathogenesis

Larvae of *S. stercoralis*, passed by the infected individuals in stools, develop into free-living adults or infective filiform larvae in the soil. The infective larvae penetrate the host's skin and enter the lungs via venous circulation. Like hookworm and roundworm larvae, they work out their way to their final habitat, i.e. small intestine (upper). The mature worms burrow into the epithelium, and release eggs, which hatch rapidly, releasing small larvae that pass in stools. The larvae in the soil (sometimes in the intestine or at the anal region) undergo morphologic changes to be ready to infect human host.

Morbidity produced by *S. stercoralis* depends on factors such as worm load, host's nutrition and immune status. Manifestations are related to the entry and course of the parasite in the body. Infrequently, it may cause larval invasion of internal organs (disseminated strongyloidiasis) which is invariably complicated by Gram-negative septicemia.

Diagnosis

Identification of the eggs in stool sample is by microscopy.

Clinical Features

Mild itching and urticaria at the site of penetration into the skin, pain abdomen, severe diarrhea, malabsorption, malnutrition, and chest manifestations simulating Loeffler syndrome are the chief presenting features.

Treatment

- **Pharmacotherapy:** Dithiazanine used to be the drug of choice. Since it may get absorbed and cause serious toxicity, it has now been replaced by ivermectin, and albendazole (Table 22.1).
- **Supportive measures:** Avoidance of bare-foot walking.

TRICHURIASIS

Infection with *Trichuris trichiura*, the so-called **whipworm**, is rather uncommon in most parts of our country though a

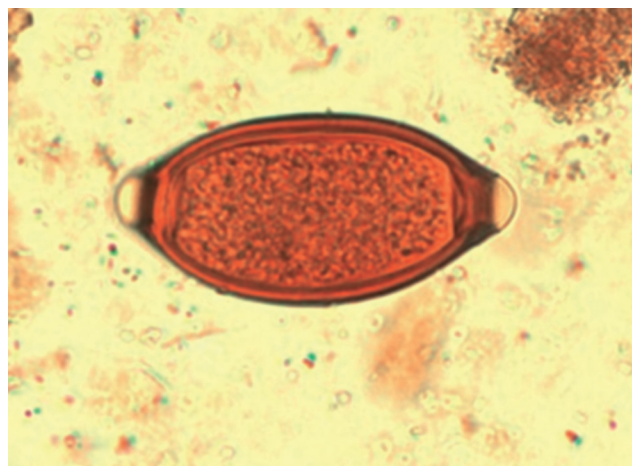


Fig. 22.5: *Trichuris trichiura*. Note the typical barrel-shaped appearance with polar plug at each end and thick shell.

very high incidence has been reported from certain other tropical and subtropical regions.

Etiopathogenesis

Embryonated eggs of *Trichuris trichiura* from the soil are transmitted by contaminated hands, food or water, flies and other insects to the human host by feco-oral route. In the small intestine, the eggs hatch and the larvae penetrate into the villi. After 3–10 days, they move down to their final habitat, i.e. cecum and ascending colon. It takes 1–3 months before maturing female worms start depositing eggs. Each adult worm sucks 0.005 mL of blood/day.

Diagnosis

Stool microscopy for *T. trichiura* eggs (Fig. 22.5).

Clinical Features

Prolonged diarrhea with blood-streaked stools, right lower abdominal pain, tenesmus, malnutrition with anemia, rectal prolapse and allergic manifestations like eosinophilia and Charcot-Leyden crystals in stools are the prominent clinical features. Children of preschool age are the ones who predominantly suffer from this infestation. The worms may be seen on the surface of the prolapsed rectal mucosa. It has been observed that children with whip-worm are especially prone to have additional roundworm and amebic infestations.

Treatment

- **Pharmacotherapy:** Eradication of whipworm is a difficult problem. Dithiazanine, though effective, is no more employed because of its serious toxicity. Of late, albendazole, mebendazole and ivermectin seem to hold promise as the drugs of choice for this infestation.
- **Supportive measures:** Hand and food hygiene.

TAPEWORMS

Hymenolepis nana infestation is quite common in India. It needs no intermediate host. *Taenia solium* infection

Table 22.2: *Taenia solium* versus *Taenia saginata*

<i>Taenia solium</i>	<i>Taenia saginata</i>
Pork tapeworm	Beef tapeworm
About 3 meter long	About 6 meter long
About 1,000 segments	About 2,000 segments
Cysticercosis is frequent	Cysticercosis is uncommon

occurs by consumption of meat of an infected pig (pork) and *Taenia saginata* that of cattle (beef). Table 22.2 gives important differences between *T. solium* and *T. saginata*.

Clinical Features

Taenia Solium (Pork Tapeworm)

Most often, parents bring the children for passing 1–2 cm long segments (proglottids) in stools or crawling over the perianal area.

Growth failure despite voracious appetite, abdominal distention and pain and recurrent diarrhea may be the presenting manifestations in some. Cysticercosis can lodge anywhere in the body. Involvement of the brain (which may show as calcification in the skull X-ray) may cause convulsion, at times, simulating a brain tumor, hydrocephalus or meningitis. Calcified nodules may be palpable in the muscles.

Taenia Saginata (Beef Tapeworm)

Clinical manifestations are like those of *T. solium*. It is less likely to cause cysticercosis. Absorption of a neurotoxin may, however, cause paresthesia and squint. Calcification may be detected in skull X-ray.

Hymenolepis Nana (Dwarf Tapeworm)

Contrary to earlier teaching, *H. nana* is now known to cause considerable morbidity in children. A follow-up of the symptomatic carriers reveals that they do become symptomatic sooner or later. Abdominal pain, loss of appetite, chronic diarrhea and malnutrition are common manifestations.

Chemotherapy

- Niclosamide is highly effective in *T. saginata* (relatively less so in *T. solium*) and *H. nana*. The recommended doses, varying with weight, are given in Table 22.1 or details, See Chapter 28 (Pediatric Neurology).
- Praziquantel (PZQ), 10 mg/kg for *T. saginata* and *T. solium* and 25 mg/kg for *H. nana* once only yields gratifying results.
- Mebendazole, 200 mg twice daily for 3 days, is effective in *T. saginata* and *T. solium* but not in *H. nana*.
- For neurocysticercosis, PZQ 50 mg/kg/day in three divided dose for 2 weeks is currently the drug of choice.
- Albendazole, 15 mg/kg/day in three divided doses for 28 days is nearly equally effective. Experience shows that results with a course of only 5–7 days are as good as with 28 days course.

NEUROCYSTICERCOSIS (NCC)

Cysticercosis is the most common parasitic disease of the central nervous system. It is caused by the larval stage of the pork tapeworm, *T. solium*. The disease has worldwide distribution. For details, See Chapter 28 (Pediatric Neurology).

HYDATID DISEASE

(Echinococcosis)

Clinically recognizable hydatid disease occurs when hydatid cysts, following infection with the larval stage of the canine tapeworm, *Echinococcus granulosus*, present as space-occupying lesions in the liver, or, infrequently, in lungs, brain, bones and spleen.

Etiology

Human infection with *E. granulosus* is acquired by ingestion of parasite eggs present in the feces of dogs or wolves who acquire infection by eating parasitized viscera of sheep or cattle. It takes several years for hydatid cysts to grow. The disease is most common in regions where sheep and cattle are raised.

Clinical Features

Manifestations appear only in a small proportion and are the result of space-occupying nature of the cysts.

- In the most common variety, **hydatid disease of the liver**, a large cystic hepatomegaly with pressure symptoms is the usual presentation.
- **Pulmonary hydatid disease** is relatively more frequent in children. Manifestations include cough, hemoptysis and dyspnea.
- **Hydatid disease of the bones** manifests as erosions and spontaneous fractures.
- **Hydatid disease of the spleen** manifests as massive splenomegaly.

Diagnosis

Diagnosis is confirmed by roentgenographic and ultrasonic examination, by Casoni test and by serologic tests.

Treatment

The drug of choice is albendazole, 15 mg/kg/day in three divided doses for 28 days. Four or five such courses at 15 day drug-free interval may be needed (Table 22.1). Medical therapy may be supplemented with surgery.

VISCERAL LARVA MIGRANS

Ingestion of toxocara eggs of nematodes infesting species other than humans is followed by hatching of larvae which invade the gut. From intestinal mucosa, they find entry into blood stream to be carried to various organs.

Clinical Features

These include recurrent episodes of respiratory infection with cough, low grade fever, wheeze; neurological disturbances; endophthalmitis, etc.

Diagnosis

- CBP shows remarkable eosinophilia.
- Chest X-ray shows lung infiltrates.
- Enzyme linked immunosorbent assay (ELISA) for toxocara antibodies clinches the diagnosis.

Treatment

First line recommended drugs are albendazole and mebendazole (Table 22.1).

FILARIASIS

Next to malaria, filariasis ranks supreme in the list of insect-borne diseases in tropical regions. In India, it is nearly a public health problem in the southern and eastern regions as also in parts of Uttar Pradesh. The disease is uncommon in north India.

Etiopathogenesis

The causative organism is *Wuchereria bancrofti* in most parts of India, except Kerala where *Brugia malayi* and *Brugia timori* occurs.

The infection is transmitted by various species of mosquito, the intermediate host. The mosquito bites the man, the definitive host. Through the punctured wound, the larvae enter the lymphatics. These larvae slowly mature and, at night, excrete microfilariae in the blood.

The infected host acts as the primary reservoir for spread of infection to others. This results from another bite of a female mosquito which sucks blood full of microfilaria. These microfilaria mature in the female mosquito into active larvae which migrate to the mouth of the mosquito, ready to be transmitted to a new host. The male worm measures about 2.5–5 cm and the female 7.5–10 cm.

The major pathologic effect is the allergic tissue response (as the larvae are present in the lymphatics), like lymphangitis, adenitis, reticuloendothelial reaction, soft edema and varices.

Clinical Features

Recurrent filarial infections are necessary for significant clinical manifestations. The various phases are:

- **Invasion:** This period is characterized by presence of transient urticaria, lymphadenitis and eosinophilia.
- **Inflammation:** Here, the patient may have acute illness with fever, lymphangitis, lymphadenitis, orchitis, epididymitis, lymphedema and delirium (filarial septicemia).
- **Obstruction:** In this phase that usually follows repeated attacks, elephantiasis of the affected parts (usually lower limbs and genitalia with *W. bancrofti* and arms and legs with *B. malayi*) is the most remarkable manifestation. Chylous ascites, chyluria or collection of milky fluid in other body cavities may also occur.
- Acute stage comprises invasion and inflammation. Chronic stage comprises obstruction.

Diagnosis

Diagnosis is usually obvious in a full-blown case in an endemic area. In the differential diagnosis, conditions such as congenital lymphedema (Milroy disease), venous thrombosis and generalized edema from other causes should be considered.

- Confirmation of diagnosis is by **demonstration of microfilaria** in the blood film at night, in the body fluid, or in lymph node biopsy.
- **Serology** may be of some help in a proportion of the cases.
- **Lymphoscintigraphy** is of value in detecting lymphatic abnormalities at a fairly early stage when the patient may not be having overt manifestations.

Treatment

Diethylcarbamazine is the drug of choice (Table 22.1). **Ivermectin**, 400 µg/kg, in a single dose may reduce microfilaremia as effectively as diethylcarbamazine. Generally, one or more repeat courses are needed for consolidation of cure. Symptomatic measures include:

- Analgesics and antipyretics
- Antihistamines/steroids for allergic reactions
- Albendazole for reducing microfilaria
- Antibiotics (doxycycline) to control superimposed bacterial infection
- Elevation of the affected body part and its dressing with ichthyol-in-glycerine.

Treatment of filarial abscess is surgery. Plastic surgery may be done in certain instances.

Prognosis

It varies with the phase of the disease and the adequacy of the therapeutic measures.

Prevention

Filariasis is a public health problem in some areas. To control it, the following two steps must be taken on war-footing.

1. Mosquito control through antilarval measures, sewage disposal and use of mosquito nets.
2. Mass treatment with diethylcarbamazine in endemic belts.

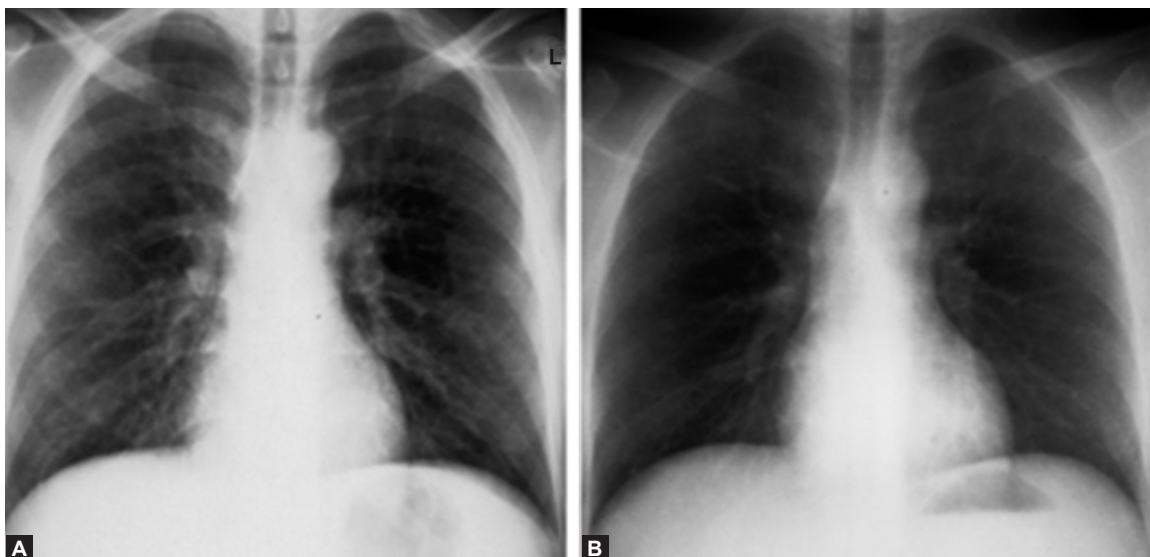
TROPICAL EOSINOPHILIA

(Tropical Pulmonary Eosinophilia, Weingarten Syndrome)

Tropical eosinophilia is a disease of doubtful etiology confined to the tropical regions such as India.

Etiopathogenesis

Today, it is believed to be a kind of allergic response to filarial infection. A gross eosinophilia, eosinophil count exceeding 2,000/mm³, is a must for this diagnostic label.



Figs 22.6A and B: Chest X-rays in tropical eosinophilia. (A) Note hilar prominence, enhanced reticular markings and basal coarse mottling; **(B)** Post-therapy with resolution of changes.

The most important pathologic lesions are nodules, 1–5 mm in diameter, scattered in the tissues such as lungs, liver and lymph nodes. The disease spares children below 1 year of age. No other age is immune, though incidence in the second year of life is the minimal.

Clinical Features

- Major manifestations are confined to the respiratory system.
- The onset is generally insidious.
- Persistent cough (often simulating asthma), some exertional dyspnea with wheezing, low fever, anorexia, growth failure and malaise are the presenting features in most cases.
- At times, vague abdominal manifestations may be present. Also, there may be enlargement of liver and lymph nodes.

Manifestations tend to persist for months at a stretch without any significant systemic disturbances.

Differential Diagnosis

Tropical eosinophilia needs to be differentiated from bronchial asthma, some forms of pulmonary tuberculosis, bronchiectasis (while it is only mild) and chronic bronchitis. Gross eosinophilia associated with certain worm infestations, like Loeffler syndrome (caused by larval ascariasis), seldom persists beyond 3 weeks.

Visceral larva migrans (caused by *Toxocara* infection) generally spare the lungs. Remaining causes of eosinophilia include hay fever, drug reaction (penicillin, sulfas, aspirin and imipramine), sarcoidosis, mycosis, Hodgkin lymphoma and certain other tumors. In the so-

called **hypereosinophilic syndrome** (very rare in children), cause of eosinophilia is not traceable and prognosis is usually grave.

Diagnosis

- Total eosinophil count varies between 4,000/mm³ and 50,000/mm³, forming almost 30–80% of all the cells. Total leukocyte count may be increased, sometimes to as high as 100,000/mm³. Erythrocyte sedimentation rate is usually high.
- Chest X-ray is abnormal in a vast majority of the cases. Increased reticular markings, coarse mottling (especially at the bases) and hilar prominence are the usual radiologic lung findings (eosinophilic lung) (Figs 22.6A and B). Peripheral lung fields are usually clear.
- High serum IgE levels, beyond 1,000 units/mL, and high titers of antimicrofilarial antibodies or demonstration of blood-borne microfilariae strongly support the diagnosis.
- Biopsy, though not usually needed, may demonstrate microfilariae in sections from lung or lymph node.

Treatment

The drug of choice, diethylcarbazine, administered in a dose of 6 mg/kg/day in three divided doses, for 10–14 days, leads to prompt improvement. If the manifestations persist for 2–3 weeks or if they recur, a second course of the drug is warranted.

Prognosis

Children with tropical eosinophilia of short duration, as a rule, show dramatic response to therapy. However, those with chronic disease show less improvement.

Multiple Choice Questions

- Spot the wrong observation:
 - Migration of larvae of *A. lumbricoides* may cause Ascaris pneumonia (Löeffler syndrome)
 - Frequently, *E. vermicularis*, causes appendicitis and salpingitis
 - Infrequently, hookworm may cause infantile disease by transmammary transmission or rarely even transplacental transmission
 - Hydatid disease of spleen presents as a massive splenomegaly
- All of the following statements about tropical eosinophilia are correct, except:
 - At least absolute eosinophil count of 10,000/mm³ is essential for this diagnosis
 - In all probability it is an allergic response to filarial infection
 - Diethylcarbamazine is the drug of choice
 - It is not the same as hypereosinophilic syndrome
- Pick up the correct observation:
 - Neurocysticercosis is caused by the larval stage of the pork tapeworm, *Taenia solium*
 - Ivermectin is effective in *H. nana* infestation
 - S. stercoralis* infection occurs through contaminated foodstuffs
 - Mebendazole is not effective in ancylostomiasis
- Cestodes include all, except:
 - Taenia solium*
 - Taenia saginata*
 - H. nana*
 - Dracunculus medinensis*
- On an average, hookworm anemia is as a result of blood oozing of approximately:
 - 0.7 mL/worm/day
 - 0.03–0.3 mL/worm/day
 - 0.01 mL/worm/day
 - 0.001 mL/worm/day

Answers

1. B 2. A 3. A 4. D 5. B

Clinical Problem-solving

Review 1

An adolescent, aged 15 years, presents with off and on diarrhea, abdominal discomfort, and easy fatigability of about a year's duration. Multiple stool microscopy reveals ova/cysts of *A. lumbricoides*, *L. giardia* and *E. histolytica*.

- Is it possible to prescribe a single drug that is effective in all the 3 infestations?
- What should be its right dose for this boy?
- What are the ADRs of this drug?

Review 2

A 6-year-old girl presents with persistent cough, exertional dyspnea (grade 1) with wheezing, slight fever, anorexia, growth failure, and vague abdominal discomfort for some 6 months. Examination shows mild malnutrition, enlargement of liver (span 10 cm) and lymph nodes. Other family members also suffer from similar complaints. A pulmonologist has ruled out diagnosis of bronchial asthma.

- What could be the most logical diagnosis?
- State two investigations you would like to have.
- Describe its treatment.

Answers

Review 1

- Yes, it is possible to treat all three infestations in this boy employing a single drug. The drug, nitazoxanide, is effective in *L. giardia*, *E. histolytica* and *A. lumbricoides*.
- The recommended dose for greater than 12 years of age is 500 mg BID for 3 days.
- Gastrointestinal upset, rash, headache, pruritus and chest pain.

contd...

Review 2

1. Tropical eosinophilia
2. Firstly, absolute eosinophil count which should be greater than 2,000/mm³ though in most cases it is much more than the cut off limit in tropical eosinophilia. Secondly, Chest X-ray which is expected to show hilar prominence, enhanced reticular markings and basal coarse mottling. Peripheral lung fields are usually clear.
3. Diethylcarbamazine is the drug of choice. It is administered in a dose of 6 mg/kg/day (in three divided doses) for 10–14 days. Outcome is prompt improvement. If the manifestations persist for 2–3 weeks or if they recur, a second course of the drug may be in place.

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OVERVIEW

Intrauterine infections include:

- T**—Toxoplasmosis
O—Others: Hepatitis B and C , HIV, varicella, syphilis, malaria, tuberculosis; even enteroviruses and paraviruses
R—Rubella
C—Cytomegalovirus
H—Herpes simplex virus
- To emphasize importance of syphilis, some experts suggest the use of the expression STORCH. Recently, the expansion of TORCH to CHEAPTORCHES has been proposed.
- C**—Chickenpox and shingles
H—Hepatitis B,C
E—Enteroviruses
A—AIDS (HIV Infection)
P—Parvovirus
T—Toxoplasmosis
O—Others
R—Rubella
C—Cytomegalovirus
H—Herpes Simplex
E—Everything else sexually transmitted
S—Syphilis

Generally speaking, certain features need to be borne in mind about TORCH infections (Box 23.1).

Box 23.1 Some noteworthy features of TORCH infections

- In mother, the signs and symptoms of offending maternal infection may be quite subtle (say, a mild influenza like illness) and, at times, may not be even noticed by the mother during the pregnancy.
- Except for syphilis, each one of them in its primary form only infects the baby.
- First trimester is the most vulnerable period for adverse effects on the fetus.
- Clinical features include abortion, intrauterine death, prematurity, IUGR, lymphadenopathy, hepatosplenomegaly, deafness, chorioretinitis, microcephaly, mental retardation, neonatal hepatitis, skeletal defects and thrombocytopenia.
- Diagnosis is clinched by serology (IgM, IgG).
- TORCH screen is helpful.
- Effective treatment is available for toxoplasmosis, syphilis, herpes simplex.
- Rubella has no treatment as yet. For CMV, available treatment is effective only up to a point.

Abbreviations: IUGR, intrauterine growth retardation; CMV, cytomegalovirus, Ig, immunoglobulin; TORCH, toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus and others.

CONGENITAL TOXOPLASMOSIS

Congenital toxoplasmosis usually occurs when the infection is acquired by an immunologically normal pregnant woman. Fetal manifestations are most severe early in gestation. However, the rate of transmission is least early in gestation and highest later in gestation.

Clinical Features

If the fetus escapes abortion, a wide variety of manifestations involving different systems may be encountered.

- Neonatal manifestations include low birth weight (LBW), hepatosplenomegaly, jaundice, anemia, meningoencephalitis, thrombocytopenic purpura and fever.
- Congenital defects include hydrocephalus or microcephaly.
- Late sequelae include chorioretinitis and mental retardation.

Triad of hydrocephalus, intracranial calcification and chorioretinitis is characteristic of congenital toxoplasmosis.

Diagnosis

- Specific immunoglobulin M (IgM) demonstration in serum of the suspected child clinches the diagnosis.
- Imaging studies (skull X-ray, Ultrasound, computed tomography {CT} scan, magnetic resonance imaging {MRI}) show calcification.

Treatment

A combination of pyrimethamine and sulfadiazine plus folinic acid should be administered for 1 year. Steroids are indicated in the presence of inflammatory lesions such as chorioretinitis involving the macula, cerebrospinal fluid (CSF) protein above 2 g/dL at birth or a generalized infection.

Prevention

- The pregnant women must avoid contact with oocytes excreted by cats and eat only well-cooked meat.
- Serologic screening and ultrasound monitoring of pregnant women contributes to prevention of congenital toxoplasmosis.
- Treatment of maternal toxoplasmosis with spiramycin (not pyrimethamine and sulfadiazine which are known teratogens) is yet another key preventive measure.



Fig. 23.1: Congenital rubella. Note the widespread maculopapular rash and petechiae in an infant with microcephaly, hepatosplenomegaly and patent ductus arteriosus.

CONGENITAL RUBELLA

There are two peaks for maternal rubella to infect the fetus causing embryopathy—first 4 weeks of gestation (risk 50%) and after 26 weeks (risk 75%), and the former being responsible for most florid embryopathy.

Clinical Features

- Rubella embryopathy may end up as abortion.
 - Neonatal manifestations include LBW, hepatosplenomegaly, icterus, hemolytic anemia, thrombocytopenic purpura, petechiae or maculopapular rash (Fig. 23.1), and osteitis.
 - Congenital defects include cardiovascular malformations, microcephaly, cataracts and microphthalmia.
 - Late sequelae include deafness, mental retardation, thyroid disorders, diabetes mellitus, renal disease, degenerative brain disease, autism spectrum disorder (ASD), etc.
- Triad of deafness, cataract and patent ductus arteriosus (PDA)** is considered classical of congenital rubella.

Diagnosis

- Demonstration of positive rubella IgM in cord or neonate's blood clinches the diagnosis.
- Imaging studies show intracranial calcification.

Prevention

The only foolproof means of prevention of congenital rubella is vaccination of the girls (future mothers) before puberty against rubella. If diagnosed in first trimester, medical termination of pregnancy is advisable.

CYTOMEGALOVIRUS (CMV) DISEASE

Transmission of the CMV from mother to fetus may occur at any stage of pregnancy.

- Neonatal manifestations include LBW, hepatosplenomegaly, jaundice, petechiae, anemia, thrombocytopenic purpura, encephalitis and sepsis-like illness with respiratory distress from pneumonia.

- Congenital defects include microcephaly, microphthalmia and retinopathy.
- Late sequelae include deafness, psychomotor retardation, seizures and cerebral calcification.

Diagnosis

- Demonstration of a positive IgM in cord or neonate's blood in first 2 weeks of life clinches the diagnosis.
- A positive quantitative polymerase chain reaction (PCR) should be done if the suspected neonate is more than 2 weeks of age as by this time CMV can be secondary to postnatal transmission.

Treatment

As yet no satisfactory treatment is available. The mortality is, therefore, high. Antiviral agents, ganciclovir and valganciclovir, may be tried in select cases (progressive CMV, deafness).

Prevention

The search for an effective CMV vaccine is in progress.

HERPES SIMPLEX VIRUS

Herpes simplex virus (HSV), usually type 2 and occasionally type 1, generally infects the infant during perinatal (intrapartum) period following contamination from mother's primary herpes of the external genitalia. A small proportion of the infants acquire the infection during intrauterine life or from mother or caretaker during postnatal period.

Clinical Features

- Abortion may be the outcome of the infrequent fetal infection occurring early in pregnancy.
- Three clinical patterns of neonatal infection are known, namely—disseminated, skin-eye-mouth disease and encephalitic disease.
 1. **Disseminated disease** is characterized by multi-organ involvement with lesions in skin, lungs, trachea, central nervous system (CNS), esophagus, kidney, adrenals, spleen, heart, etc. Manifestations, which start from fourth to tenth day after birth, mimic fulminant septicemia. These include fever, apnea, respiratory distress, seizures, lethargy, irritability, conjugated hyperbilirubinemia, shock disseminated intravascular coagulation (DIC) and vesicles.
 2. **Skin-eye-mouth disease** is characterized by cutaneous vesicles and ocular lesions (keratoconjunctivitis, late chorioretinitis, microphthalmia, cataracts). If not treated with antiviral therapy, this type may progress to disseminated disease.
 3. **Encephalitic disease** (isolated), due to retrograde axonal transmission of virus to CNS and not viremia, is characterized by pyrexia, irritability, lethargy, change in sensorium (even coma), seizures, bulging fontanelle, high-pitched cry and focal temporal lobe lesions on CT scan, or electroencephalogram (EEG).

Diagnosis

Herpes simplex virus can be diagnosed by the following methods:

- Tzanck smear made from skin lesions.
- Tissue cultures obtained from vesicles, nasopharyngeal or throat swabs, urine, stool, tracheal secretions, duodenal aspirate and CSF and PCR.

Treatment

Two antiviral agents, intravenous (IV) acyclovir and vidarabine, are recommended. Acyclovir is particularly superior to vidarabine in HSV encephalitic disease. As soon a diagnosis is made in the neonate, IV acyclovir should be started. Topical antiviral agents for ophthalmic involvement include vidarabine, idoxuridine and trifluorothymidine.

Prevention

Mothers with genital herpes should have delivery by elective cesarean section. The latter should preferably be done in mothers with unruptured membranes or within 4–6 hours of rupture of membranes.

Prognosis

Disseminated and encephalitic herpes have worse prognosis than skin-eye-mouth herpes. HSV type I encephalitis has a better outcome than HSV type 2 encephalitis.

CONGENITAL SYPHILIS

Maternal syphilis, even in first trimester, may cause transplacental infection to the fetus, the risk being almost 100%. During passage through the birth canal, risk is certainly there, but only minimal.

Clinical Features

- Maternal syphilis is notorious for causing recurrent abortions
- Syphilis may cause abortion, still birth or hydrops fetalis
- Early manifestations include:
 - Skin lesions (bullous, maculopapular or condylomatous over palms and soles), rhinitis or snuffles (frequently blood-stained discharge), pneumonia alba (also called “white pneumonia” since lungs are firm and pale, owing to the presence of inflammatory cells and fibrosis in the alveolar septa), jaundice, hepatosplenomegaly, and generalized lymphadenopathy.
 - Coombs negative hemolytic anemia, thrombocytopenic purpura, bony lesion (osteitis, osteochondritis, pseudoparalysis usually unilateral involving upper-limbs), and perioral and perianal ulcerations are other findings.
 - Intrauterine growth retardation/restriction (IUGR) is invariably present.
 - Head may be microcephalic or hydrocephalic.
- Late manifestations (usually after 2 years of age) include:
 - Depressed nasal bridge
 - Frontal bossing

- Notched central incisors
- Interstitial keratitis and saber shins.

Diagnosis

It is based on:

- Clinical suspicion
- Examination of placenta
- Quantitative venereal disease research laboratory (VDRL) serology
- Radiology of bones and
- CSF.

Treatment

- If CSF is normal, procaine penicillin, 50,000 units/kg/day intramuscular (IM) for 10–14 days suffices. Alternatively, ceftriaxone may be employed.
- If CSF is abnormal, crystalline penicillin, 100,000–150,000 units/kg/day in 2 or 3 divided doses (IM, IV) for at least 10 days is required.

PERINATAL HIV/AIDS

A human immunodeficiency (HIV) positive mother may pass on the infection to the infant *in utero*, during delivery or through breastfeeding. The risk following breastfeeding is only 14%, but the overall risk varies from 50% to 60%. Existence of vitamin A deficiency in the mother boosts the risk of vertical transmission 3–4 times.

Clinical Features

Usually, the infant is asymptomatic at birth and may remain so during the first 6 months. The facial dysmorphism includes hypertelorism, prominent box-like forehead, short nose with depressed bridge of nose, oblique eyes with long palpebral fissures and blue sclerae, patulous lips and prominent triangular philtrum.

Differential diagnosis should include fetal-alcohol syndrome and familial traits.

Diagnosis

Seropositivity alone, unless it persists beyond 15 months, cannot be counted for establishing diagnosis of perinatal HIV infection. On the other hand, actually infected infants may turn out to be seronegative at 15 months. The enzyme-linked immunosorbent assay (ELISA) and Western blot tests, therefore, have limited diagnostic value in perinatal acquired immunodeficiency syndrome (AIDS).

Culture and PCR are recommended for early and dependable diagnosis of perinatal HIV infection.

Management

Good nursing care and good nutrition constitute the mainstay of management of perinatal HIV infection. Ideally, in prosperous families, breastfeeding should be withheld. However, in the underprivileged, exclusive breastfeeding needs to be continued because of its unmatched nutritive

408 and anti-infective values and only limited risk of passing the HIV to the baby.

To safeguard against intercurrent infections, IV immunoglobulins are advocated. Cotrimoxazole as a prophylaxis against *Pneumocystis carinii* (new name *Pneumocystis jiroveci*) is in order.

To prevent candida esophagitis, oral application of ketoconazole early in course of disease may be helpful. The use of specific antiviral agent, azidothymidine (AZT or zidovudine) and nevirapine in perinatal HIV infection has shown encouraging results.

VARICELLA ZOSTER VIRUS INFECTION

Mode of Infection

Infection is by direct physical contact, or air-borne contact with droplets of respiratory secretions after the primary infection resolves. The virus enters the latent phase and remains dormant in the thoracic sensory ganglia. Reactivation may occur along the sensory dermatome to cause herpes zoster or *shingles*.

Clinical Features

- **Maternal manifestations** include rash, viral pneumonia, meningitis, and encephalitis.
- **Fetal manifestations** include limb hypoplexia, paresis, microcephaly, hydrocephaly, microphthalmia, duodenal stenosis, jejunal dilatation, microcolon, atresia of sigmoid colon, cataract, chorioretinitis, seizures, hypotonia, Horner's syndrome, etc.

Diagnosis

- Polymerase chain reaction (PCR) to detect viral DNA in cord blood sample of the infected infants.
- Varicella zoster virus (VZV) specific IgM and IgG antibodies can be detected at an early stage.

Treatment

- In case of severe maternal infection antiviral acyclovir can be used.
- For fetal infection, varicella zoster virus immunoglobulin (VZG 12510) is used in combination therapy with acyclovir.

Multiple Choice Questions

1. Triad of cataract, congenital heart disease and deafness (sensorineural) usually occurs in:
 - A. Toxoplasmosis
 - B. Galactosemia
 - C. Congenital rubella syndrome
 - D. Down syndrome
2. Drug of choice in CMV pneumonia:
 - A. Ribavirin
 - B. Acyclovir
 - C. Ganciclovir
 - D. Amantadine
3. Most frequent manifestation of toxoplasmosis:
 - A. Intracranial calcification
 - B. Fundal lesions
 - C. Motor deficit
 - D. High CSF protein
4. Most frequent ophthalmic lesion in toxoplasmosis is:
 - A. Retinitis pigmentosa
 - B. Chorioretinitis
 - C. Cataracts
 - D. Corneal sclerosis
 - E. Corneal opacity
5. The triad of "seizures, chorioretinitis and calcification in brain" is seen in each of the following, except:
 - A. Congenital rubella
 - B. Congenital toxoplasmosis
 - C. Congenital cytomegalovirus
 - D. Congenital varicella

Answers

1. C 2. C 3. A 4. B 5. D

Clinical Problem-solving

Review 1

A 3-month-old infant, born IUGR to a mother with bad obstetric history, presents with failure to thrive, microcephaly, patent ductus arteriosus, cataracts and hepatosplenomegaly.

1. What according to you should be the diagnosis?
2. When did, in your opinion, the intrauterine infection occur?
3. Is this infant liable to develop further problems?

Review 2

A 6-day-old neonate presents with pyrexia, irritability, progressive lethargy, seizures, bulging fontanel and high-pitched cry. CT scan reveals focal temporal lobe lesions.

1. What is the most likely diagnosis?
2. Is it secondary to viremia?
3. Treatment?

Answers

Review 1

1. Congenital rubella syndrome.
2. Since there is evidence of significant embryopathy, it seems intrauterine infection occurred in the first trimester, in all probability first 4 weeks.
3. Of course, further manifestations may be in the form of late sequelae such as deafness and mental retardation. There is high incidence of thyroid disorders, diabetes mellitus, renal disease, degenerative brain disease and autism spectrum disorder (ASD) in these children.

Review 2

1. Encephalitic disease caused by herpes simplex virus.
2. No. It is a retrograde axonal transmission of virus to CNS and not viremia.
3. Two antiviral agents, intravenous (IV) acyclovir and vidarabine, are recommended. Acyclovir is particularly superior to vidarabine in HSV encephalitic disease. As soon a diagnosis is made in the neonate, IV acyclovir should be started.

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NOSOCOMIAL INFECTIONS

(Hospital-Acquired Infections)

Definition

According to the Center for Disease Control and Prevention (CDC), these are infections which develop within the hospital or are produced by microorganisms acquired during hospitalization and manifest after discharge. Essentially, these are not present at the time of admission to the hospital. Thus, all infections identified between 48 hours following admission and 48–72 hours following discharge should be treated as **nosocomial infections**.

These infections may afflict not only the patients, but also staff members, volunteers, visitors and attendants, etc. having contact with the hospital. Some of the affected individuals may manifest symptoms after discharge from the hospital, e.g. hepatitis B and some other infections of the newborn.

In order to monitor the prevalence of nosocomial infections, CDC has recommended setting up of National Infection Surveillance (NNIS) program in each and every country.

Types and Frequency

Nosocomial infections are quite a problem in intensive care unit (ICU) (both neonatal intensive care unit {NICU} and pediatric intensive care unit {PICU}) caring for critically sick patients. According to conservative estimates, their incidence ranges from 2.8% to 21.6%. Almost 10% of hospital mortality is attributed to nosocomial infections. Table 24.1 gives relative prevalence of different types of nosocomial infections.

Table 24.1: Relative prevalence of different types of nosocomial infections

Type	Prevalence
Blood-borne (sepsis)	28%
LRTI (bronchopneumonia, lobar pneumonia)	22%
UTI	18%
Miscellaneous	32%

Abbreviations: LRTI, lower respiratory tract infection; UTI, urinary tract infection.

Box 24.1 Determinants of nosocomial infections

- Level of invasive monitoring (intravascular catheters, urinary catheters, endotracheal tubes, nasogastric tubes)
- Irrational antimicrobial therapy
- Severity of illness
- Nature of diagnostic/investigative procedures
- Level of hygienic measures (hand hygiene)
- Immunological status of the inmates.

Risk Factors

Box 24.1 lists the determinants of nosocomial infections.

Etiologic Considerations

All infections in newborns delivered in the hospital need to be considered acquired except those caused by organisms reaching the baby from the mother at or before the time of birth. This is true in early onset of systemic sepsis caused by *Escherichia coli*, Group B *Streptococci* (GBS) and *Listeria monocytogenes*, etc. Congenital infection can be due to cytomegalovirus and toxoplasma. Eye infections may be due to *Gonococcus* and *Chlamydia*. Septicemia and meningitis are quite common in first week of life.

Measures employed to increase the survival rate in small babies have added greatly to the risk of nosocomial infections, e.g. intravenous (IV) drip, assisted respiration, parenteral nutrition, lavish use of broad spectrum antibiotics and extensive surgical maneuvers on babies with congenital malformations. Sepsis rate in NICU is among the highest anywhere in the hospital.

Infections appearing after first few days of life are predominantly caused by enterobacteria, *Pseudomonas aeruginosa* and other nonfermenters. *Flavobacterium meningosepticum* and *Citrobacter koseri*, however, appear to cause meningitis in the newborn.

Stay of the neonate in the hospital for more than a week is likely to lead to Staphylococcal skin infection of both vesicular and pustular type. It often occurs in epidemics associated with single strain of *Staphylococcus aureus*.

In recent decades, neonatal necrotizing enterocolitis has come to be recognized as an important hazard to the lives of premature babies in special care neonatal unit (SCNU). The condition does not start until oral feeding is initiated. According to a hypothesis, hygienic precautions taken in SCNU tend to lead to homogeneity in the gut flora in which only one or very few bacterial strains may multiply unchecked during first few days of life.

Diarrheal disease of the newborn may be caused by *E. coli*, *Salmonella*, *Vibrio cholerae*, *Shigella*, *Campylobacter*, rotavirus, etc. According to one report of infection with *Mycobacterium tuberculosis*, babies born in obstetric unit had converted to tuberculin positive at an extraordinarily high rate. This could only be explained by acquisition of hospital infection.

The other organisms causing neonatal nosocomial infections are *Bordetella pertussis*, *Hemophilus influenzae*, *Corynebacterium diphtheriae*, *Clostridium tetani*, *Hemophilus influenzae*, virus (A, B, non-A, non-B), rubella, influenza, respiratory syncytial, *Candida*, *Mucor* and *Pneumocystis carinii*.

Mode of Transmission

- **Contact spread:** Contact with a number of contaminated inanimate objects serves as a source of transmission of nosocomial infections in children, e.g. rectal thermometer, feeding bottle, nipples, aspiration and suction material and equipment, disinfectants, venous and arterial catheters, renal dialysers, etc.
- **Common vehicle spread:** Here contaminated inanimate vehicle serves as the vector for transmission of infectious agent to multiple individuals, e.g. infected food, blood and its products, IV fluids, etc.
- **Airborne spread:** This involves an organism that has a true airborne phase in its route of dissemination which usually involves a distance of more than several feet between the source and the victim, e.g. tuberculosis, *Staphylococcus* infection, salmonellosis, etc.
- **Vector-borne spread:** Vector-borne transmissions, both external and internal, can cause nosocomial infections. By external vector-borne transmission is meant mechanical transfer of microorganisms on body or appendages of the vector, e.g. *Shigella* and *Salmonella* which spread in this way through flies. Internal vector-borne transmission includes harborage (*Yersinia pestis*) and biologic transmission (malarial parasite).

Common Nosocomial Infections

- Lower respiratory tract infections (LRTI), e.g. pneumonia, pulmonary tuberculosis, pulmonary aspergillosis, *Chlamydia*, *P. carinii*, etc.
- Surgical wound infection following diagnostic and therapeutic procedures, e.g. urinary tract catheterization or instrumentation, tracheostomy, continuous IV therapy, surgical wounds, etc. Pathogens of wound infection are *Staphylococcus aureus*, *E. coli*, *P. aeruginosa*, *Proteus*, *Bacteroides*, etc.
- Gastroenteritis; organisms responsible are *Shigella*, *Salmonella*, rotavirus, *Yersinia*, *Vibrio cholerae*, *Campylobacter* and *Clostridium difficile*.
- Intravenous cannula-associated infections; organisms responsible are *Klebsiella*, *Staphylococcus aureus*, *Citrobacter*, *Candida albicans*, etc.

Investigations

- Nose and throat swabs of all contacts must be processed.
- Skin swabs from suspected carriers should be rubbed over the chosen site.
- Floor, furniture, baths, operations, tables, moistened swabs, etc. may also be source of infection. Hence, a moistened swab is rubbed over wide area of the surface and then seeded on blood agar or appropriate selective media.
- Textile, linen, cotton and dressing may harbor pathogens capable of causing hospital infection. Small portion of each of them, if available, may be dipped into bottles containing broth and cooked meat broth.
- Exposure of blood agar plates in pairs at various sites in the operation theater to find risk of aerial contamination of wounds.

Preventive and Control Measures

Infection control measures are the key to prevent and control nosocomial infections

Specific

- Provision of graded care facilities, including an observation unit, an ICU and an intermediate care or long-term growth unit.
- Infants with infections that can spread by airborne route must be separated from other infants, preferably out of nursery area.
- Use of prophylactic antibiotics in high-risk infants, especially with respiratory support and endotracheal intubation.
- Surveillance program, using multiple techniques to detect infection and related problems within a nursery and to detect infection pattern, should be implemented.
- Use of gowns, caps and masks.*
- Proper hand washing.
- Critical evaluation of new procedures and techniques into the nursery, e.g. *Staphylococcus enterocolitis* in infants having indwelling nasoduodenal feeding catheter passed through nares are colonized with *Staphylococcus aureus*.

General

- As far as possible, provision of separate cubicle type space for each patient with barrier nursing should be provided. Glass pane partition is usually adequate.
- Division of the ward into sections with clean and septic cases kept separately in groups.
- Highly infectious cases such as measles, pertussis, etc. should be kept in isolation rooms.
- Each section should have facilities for intensive care and resuscitation so that undue movement of equipment or patient himself from one section to another can be avoided.
- It is better to have wheel cots so that the entire cot and patient rather than only the patient can be moved if

* There is evidence that, if compliance regarding proper hand washing becomes 100%, gowns, caps and masks may not be needed.

required. It should be the policy to retain the same cot during the whole hospital stay of the child. If possible, the cot should be washed with soap and water and carbolized with phenol after the patient is discharged. Bed sheet, pillow cover, etc. also need to be treated in this way. A pottie with opened plastic bag should be provided with each cot.

- Ward floor, toilet, wash basins, sinks, etc. need to be kept clean by frequent washing, etc. It is better to have foot-operated taps and two-way swing doors to prevent frequent touching.
- Health education session for the parents/attendants as also for the staff.

Therapy chiefly consists of intensive antibiotic cover, nutritional rehabilitation, and, if the need arises, plastic surgery later.

A Hospital Infection Control Committee (HICC) is mandatory in order to formulate and implement policies and actions that should be adhered to intensive care settings to minimize the incidence of nosocomial infections.

ANAEROBIC INFECTIONS

Etiopathogenesis

Anaerobic bacteria are agents that poorly tolerate oxygen. Two types are known:

1. **Obligate:** They fail to grow on blood agar plate incubated aerobically, even when generous supply of carbon dioxides is made available.
2. **Facultative:** They manage to survive in the presence of oxygen. Their growth is, however, better when the oxygen supply is reduced. These bacteria form a part of normal human flora, particularly in the buccal cavity, gastrointestinal tract (GIT), vagina and skin. There is distinct predominance of obligate anaerobes. Anaerobes may be categorized as per Box 24.2.

Box 24.2 Classification of anaerobes

- **Bacilli (Gram +ve)**
 - **Spore-forming:** *Clostridium tetani*, *Clostridium perfringens*, *Clostridium botulinum*, *Clostridium novyi*, *Clostridium septicum*, *Clostridium ramosum*.
 - **Nonspore-forming:** *Lactobacillus*, *Bifidobacterium*, *Arachnia bacterium*, *Propionibacterium*.
- **Gram -ve (only nonspore-forming)**
 - **Bacteroides:** *Bacteroides fragilis*, *Bacteroides oralis*, *Bacteroides melaninogenicus*, *Bacteroides corrodens*.
 - **Fusobacterium:** *Fusobacterium nucleatum*, *Fusobacterium vanum*, *Fusobacterium necrophorum*, *Fusobacterium mortiferum*.
- **Cocci (Gram +ve):** *Peptococcus*, *Peptostreptococcus*, *micro-aerophilic cocci*.
- **Cocci (Gram -ve):** *Veillonella*, *Acidaminococcus*, *Megasphaera*.

Infection with anaerobes may occur by any of the following mechanisms:

- Aerobes destroying healthy tissue, thereby making the previously well-oxygenated healthy sites vulnerable to establishment of anaerobic infection.
- Removal of oxygen or addition of reducing substances, thereby reducing the oxygen reduction potential.
- Removal of aerobes.

Pathology

Major pathologic findings in anaerobic infection consist of abscess formation and widespread tissue destruction. Any part of the body may be involved by anaerobic infections.

Clinical Features

- Anaerobic infection of the upper respiratory tract usually takes the form of periodontal inflammation, periapical abscess, osteomyelitis of mandible or maxilla, chronic sinusitis, otitis media, mastoiditis, peritonsillar or retropharyngeal abscess, parotitis, cervical adenitis, etc. In Vincent angina and Ludwig angina, anaerobes (*Fusobacteria*) are particularly important.
- Anaerobic infection of the lower respiratory tract may present as necrotizing pneumonia, putrid empyema or lung abscess.
- Anaerobic infection of the central nervous system (CNS) usually manifests as brain abscess, subdural empyema, or septic thrombophlebitis of venous sinuses or cortical veins.
- Anaerobic infection of the GIT (usually lower) presents in the form of manifestations which depend upon the nature of the primary lesion as also on the subsequent localization of disease process.
- Manifestations of anaerobic septicemia include pyrexia, jaundice, hemolytic anemia and shock. There is leukocytosis.
- Other manifestations of anaerobic infection include septic arthritis, osteomyelitis, urinary tract infection (UTI), liver and subphrenic abscess adenitis and involvement of soft tissue and skin.

Diagnosis

Anaerobic infection may be anticipated in the following situations.

- Birth after prolonged rupture of membranes, amnionitis or obstetrical delivery (neonatal anaerobic infection).
- Peritonitis or septicemia associated with intestinal obstruction or perforation, appendicitis, cholecystitis or gastroenteritis.
- Congenital or acquired disorders in which response to infection is impaired. Clinical clues to anaerobic infection include foul smelling discharge, necrosis, gangrene, infection close to mucosal surface, endocarditis with negative blood cultures, septic thrombophlebitis or obscure icterus with bacteremia. Also important are clues such as infection that persists or follows prolonged use of gentamicin or other aminoglycosides, infection with tissue destruction as in injury or malignancy, or infection after human or dog (in fact, any animal) bite.

Definite diagnosis is by cultures from the infected site. For rapid diagnosis, immunofluorescence assay or gas liquid chromatography of purulent material may be done.

Treatment

Pending results of culture and sensitivity, an appropriate therapy must be started, depending upon the type of

Table 24.2: Range of activity of antimicrobials in anaerobic infections

Range of activity	Antimicrobials
Nearly always	Metronidazole (except in actinomyces), active chloramphenicol, β -lactamase antibiotics combined with β -lactamase inhibitors (ticarcillin, ampicillin, subclavate, clavulanic acid)
Usually active	Clindamycin, cefoxitin, antipseudomonas penicillins
Variably active	Penicillin, vancomycin

Table 24.3: Antimicrobials recommended for various anaerobic infections

Infection according to site	Recommended antimicrobial agent(s)
Orofacial	High dose intravenous penicillin
Pleuropulmonary	Clindamycin
Peritonitis	Clindamycin, cefoxitin, metronidazole
Brain abscess	Metronidazole, chloramphenicol
Salpingitis	Cefoxitin
Tubo-ovarian abscess	Clindamycin, metronidazole or cefoxitin

anaerobic infection that can generally be predicted from the site of infection. A combination of penicillin with chloramphenicol suffices in most situations. Addition of metronidazole (O, IV) is claimed to yield still better results. Table 24.2 gives the pattern of activity of various antimicrobial in anaerobic infections.

Table 24.3 gives recommendations on use of **antimicrobials** in various anaerobic infections based on site of infection, epidemiology and sensitivity pattern. Aminoglycosides, cephalosporins and quinolones are ineffective against anaerobes. Penicillin is ineffective in *B. fragilis* which is an important anaerobe not only in infections below the diaphragm, but also in 15–25% of lower respiratory infections. Besides antimicrobial therapy, approach to therapy in anaerobic infections must address to debridement, resection, aspiration and drainage of cavities containing septic material.

Prognosis

It depends on type of disease with anaerobic infection, rapidity with which appropriate therapy is started and age of the patient. Mortality is relatively higher in subjects suffering from extensive tissue necrosis with inadequate debridement or necrotizing enterocolitis and in newborns. In the neonates, 15–20% mortality occurs.

OPPORTUNISTIC INFECTIONS

These include:

- Infections due to ordinarily nonpathogenic bacteria or fungi
- Unusual clinical infections with common pathogens.

In Normal Host

Saprophytic microorganisms that form the indigenous flora of the host or are commonly associated with the

neonatal period may turn opportunistic causing clinical infection in normal, healthy infants and children.

Examples include:

- *Bacteroids*—abscesses, septicemia, peritonitis
- *Bacillus subtilis*—abscess, cellulitis, conjunctivitis, septicemia
- *Diphtheroids*—endocarditis, meningitis
- *Lactobacillus*—lung abscess.

In Susceptible Host

Derangement of the host defense as a result of an identifiable congenital, acquired or environmental defect.

Host Compromised by Changes in the Skin or Mucous Membranes, or by Anatomic Defect

Here the barriers to infection are bypassed or compromised, producing conducive environment for opportunistic infections.

In various shunts (cerebrospinal fluid {CSF}, renal dialysis), opportunistic organisms mostly isolated are *S. epidermidis*, *S. aureus*, *Bacillus species*, and diphtheroids. Manifestations include fever, erythema around the tubing employed for shunt, and hypocomplementemic glomerulonephritis. Treatment, pending sensitivity report, should be with penicillin and chloramphenicol, or chloramphenicol and a cephalosporin, together with removal of the shunt in majority of the cases.

Intravenous catheterization, particularly for total parenteral nutrition, may cause local thrombophlebitis, bacteremia or fungemia by opportunistic organisms such as *S. epidermidis*, *Bacteroids*, *Mimeae*, *Pseudomonas*, *Candida* and *Cryptococcus*. If clinical signs and positive cultures persist, suitable antibiotic therapy should be instituted.

Use of **inhalation therapy equipment**, especially in newborns, may lead to infection with opportunistic organisms such as *Pseudomonas* and *Serratia*. **Urethral catheterization** may predispose an individual to opportunistic infection of the urinary tract with *Pseudomonas species*, *Serratia*, *Herellea*, *S. epidermidis* or *Candida*.

Burns may lead to opportunistic infection with *Pseudomonas*, *Serratia*, *Staphylococcus*, *Candida* or *Mucor*. The possible causes include change in ecology of skin flora and physiochemical properties of skin, neutrophil dysfunction, abnormal responses to antigenic stimulation, impairment of delayed hypersensitivity, long-term administration of antibiotics and prolonged intravenous or urethral catheterization.

Dermal sinus tracts that communicate with neural tissue or subarachnoid space may lead to meningitis with organisms such as *S. epidermidis* or diphtheroids. **Cardiac defects** (both congenital and acquired) predispose the damage tissue to act as nidus for opportunistic infection with *Streptococcus viridans*, *Corynebacterium*, *Pseudomonas*, or non-pathogenic *Neisseria*.

Surgery, especially cardiac surgery predisposes to infection because of prophylactic use of antibiotics which alter the normal flora or nidus of infection provided by foreign bodies inserted. *Staphylococcus epidermidis*, *Diphtheroids*, *Mimeae*,

414 *Pseudomonas*, *Candida* and *Aspergillus* are the opportunistic organisms that may produce disease.

Host Compromized by Inherited/Acquired Defects Affecting Defense

B cell defects are frequently accompanied by recurrent infections, often due to opportunistic organisms such as bacterial pathogens and *Pseudomonas*. Treatment consists of giving gamma globulin 1.4 ml/kg (intramuscular {IM}), drainage of abscess if present and antibiotic therapy depending upon the etiologic agent. Prevention consists in giving gamma globulin 0.7 ml/kg/month (IM), vigorous attention to postural drainage in chronic respiratory disease, and prophylactic use of penicillin or ampicillin in selected cases demonstrating recurrent middle ear or lung problem.

T cell defects also are often complicated by recurrent opportunistic infections with *Mycobacterium*, *Listeria*, *Nocardia*, cytomegalovirus, Varicella, *Cryptococcus*, *Candida*, *Pneumocystis* and *Strongyloids stercoralis*. Treatment consists of giving a narrow-spectrum antimicrobial (depending on the responsible agent) application of topical and nonabsorbable antimicrobial agent and incision and drainage of abscess, if any. Prevention consists of prophylactic administration of cotrimoxazole for prevention of *Pneumocystis carinii* pneumonia, protective environments for certain patients, oral nonabsorbable antimicrobial agents to lower concentration of GIT flora, and careful screening for tuberculosis. No live vaccine should be given to these patients.

Combined immunodeficiency syndromes are also vulnerable to opportunistic infections with organisms such as bacteria, fungi, viruses and *Pneumocystis*. In addition to gamma globulin, all the therapeutic and preventive measures required in T cell defects are indicated in these patients too.

In **immunosuppression** resulting from drug therapy, infection with aerobic Gram-negative organisms occurs more commonly and may cause significant morbidity and infection from *Pseudomonas*, *Klebsiella*, *E. coli*, *Herellea*, *Serratia*, herpes simplex, Varicella zoster, cytomegalovirus, Epstein-Barr virus (EBV), papovirus, hepatitis virus, *Candida*, *Aspergillus*, *Mucor* and *Cryptococcus*.

Transplantation may *per se* predispose the host to infection and also through use of immunosuppressive therapy. Opportunistic organisms isolated usually include *Staphylococcus*, *Pseudomonas*, *Klebsiella*, *Candida*, *Aspergillus*, *Nocardia*, *Pneumocystis*, cytomegalovirus, hepatitis virus, herpes simplex and varicella zoster.

Malignancy is often complicated by infection which may prove a terminal event. Opportunistic organisms in malignancy include *Pseudomonas*, *Klebsiella*, *E. coli*, *Listeria*, *Mycobacterium* (Table 24.4). Probable mechanisms include granulocytopenia, reduced chemotaxis, reduced bacterial activity of neutrophils, lymphopenia, defective cellular response and defective antigenic response to challenge.

Malnutrition renders the host vulnerable to opportunistic infection with organisms such as measles virus, herpes or varicella zoster virus and *Mycobacterium*. The susceptibility is attributed to impaired T cell function, reduction in complement activity, impaired migration of phagocytes and reduced bactericidal activity.

Collagen diseases are frequently complicated by infections with *Candida*, *Mucor*, *Aspergillus*, *Pneumocystis*, *Diphtheroids*, *Listeria*, *Serratia*, *Staphylococcus*, *Nocardia*, cytomegalovirus, herpes virus, Varicella Zoster, etc. Host defence is reduced because of involvement of reticuloendothelial system and use of immunosuppressive agents.

Table 24.4: Microbial pattern of pediatric malignancy

Clinical situation	Common microbial pattern
Fever due to septicemia in ALL	Gram-negative organisms
Protracted fever in ALL during relapse	Fungal organisms
Infection in CLL	Gram-positive organisms
Infection in multiple myeloma	Gram-positive organisms
Infection in CLL and multiple myeloma	Gram-negative organisms with neutropenia
Infection in Hodgkin lymphoma	<i>Listeria</i> , <i>Salmonella</i> , <i>Brucella</i> , <i>Mycobacteria</i> , <i>Cryptococcus</i> , <i>Pneumocystis</i>

Abbreviations: ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia.

Multiple Choice Questions

- Spot the wrong entry about nosocomial infections?
 - Almost 10% of hospital mortality is attributed to nosocomial infections
 - All infections identified between 24 hours following admission and 48 hours following discharge
 - In Vincent angina and Ludwig angina, anaerobes (*Fusobacteria*) are particularly important
 - Infection control measures are the key to prevent and control nosocomial infections
- Infection of the CNS manifesting as brain abscess, subdural empyema, or septic thrombophlebitis of venous sinuses or cortical veins is most likely:
 - Opportunistic infection
 - Anaerobic infection
 - Nosocomial infection
 - None of these
- True observations about anaerobic infections include all, except:
 - Anaerobic bacteria are agents that poorly tolerate oxygen
 - Major pathologic findings in anaerobic infection consist of abscess formation and widespread tissue destruction

contd...

- C. Facultative anaerobes have a distinct predominance over obligate anaerobes
- D. Metronidazole is nearly always active against anaerobes with the exception of actinomyces
- 4. True observations about opportunistic infections include all, except:
 - A. Infections due to ordinarily nonpathogenic bacteria only
 - B. Malnutrition renders the host vulnerable to opportunistic infection with organisms such as measles virus, herpes or Varicella zoster virus and *Mycobacterium*
 - C. Protracted fever in ALL during relapse is a conducive situation for fungal infection
 - D. Opportunistic organisms in malignancy include *Pseudomonas*, *Klebsiella*, *E. coli*, *Listeria*, and *Mycobacterium*
- 5. Pick up the correct statement:
 - A. Nosocomial infections afflict only the patients
 - B. Irrational antimicrobial therapy, poor hand hygiene, poor immunologic status of the patient, etc. are among the important determinants of nosocomial infections
 - C. Anaerobic infection of the lower respiratory tract may present as pleural effusion
 - D. Susceptibility of malignancy to opportunistic organisms is attributed to impaired B cell function

Answers

1. A 2. B 3. C 4. A 5. B

Clinical Problem-solving**Review 1**

A 5-day-old infant, weighing 2.9 kg, has ruptured membranes overlying meningocele. As the pediatric surgeon is contemplating a surgical intervention, the baby develops convulsions, refusal of feed, and cold, clammy skin with sclerema.

1. What is the diagnosis?
2. What are the likely opportunistic organisms?
3. What is the modus operandi in development of meningitis?
4. What is the prognosis?

Review 2

A 10-year-old boy remains admitted in the Pediatric Intensive Care Unit for complicated dengue where he receives platelet transfusions and symptomatic and supportive treatment. After 1 week, he is discharged as "cured". Just within 36 hours, he returns to the hospital with pyogenic liver abscess.

1. Could this development be a part of dengue manifesting after the primary illness is checked?
2. If not, what can be the explanation for development of pyogenic liver abscess in this child?
3. What should be recommended antimicrobials in this situation?

Answer**Review 1**

1. Neonatal sepsis with meningitis
2. *S. epidermidis* or diphtheroids
3. Through a communication from dermal sinus tract, the opportunistic organism gain access to the CNS
4. Poor

Review 2

1. Very unlikely that it is related to dengue
2. Since the child is back to hospital within 36 hours of discharge, chances are that nosocomial infection acquired during his stay in the PICU has caused pyogenic liver abscess. An infection manifesting within 72 hours of discharge, as per standard normal, is to be considered "nosocomial"
3. A combination of beta-lactam antibiotics with beta-lactamase inhibitor and metronidazole is the best choice in the given situation

FURTHER READING**JOURNAL ARTICLES/BOOK CHAPTERS**

1. Lodha R, Natcha UCM, Nanda M, Kabra SK. Nosocomial infections in pediatric intensive care units. *Indian J Pediatr* 2001;68:1063–1070.
2. Raynold ASD. Infection control in NICU and PICU. *Eur Bull Infect Dis* 2015;4:67–74.

BOOK/MONOGRAPH

1. Kelly E, Kelly JE. *Infectious Diseases*, 2nd edn. Boston: Academic Press 2015.

OVERVIEW

Fever or pyrexia is defined as an increase in the core body temperature and is a warning sign that some underlying problem is in operation. The cut-off point for fever is a rectal temperature of 38°C (100°F) or more. If it exceeds 40°C (104°F), the term **hyperpyrexia** is employed. It is only a symptom as a result of production of endogenous pyrogens like interleukin- β , interferon- γ and lipid mediators like prostaglandin E₂. These tend to raise the body temperature by changing the temperature set-point in the anterior hypothalamus.

Understandably, true fever is associated with alteration in hypothalamic set-point. In the so-called **heat illness**, e.g. heat stroke, hyperthyroidism, malignant hyperthermia, anhydrotic ectodermal dysplasia, drugs such as phenothiazines and anticholinergic agents, elevated temperature is not a true fever since in it there is no change in the hypothalamic set-point. Noteworthy adverse effects of fever are listed in Box 25.1.

Fever may be of short or prolonged duration. It may also be with focus (say a rash) and without focus. Furthermore, it may remain without an identifiable cause on simple investigation, the so-called **fever of unknown origin** (FUO). Since, in India both Celsius and Fahrenheit system continue to be employed in lieu of temperature, it is advisable to bear in mind the relationship between the two systems (Table 25.1). For instance, it is good to remember that 37°C = 98.6°F, 38°C = 100.4°F, 40°C = 104°F.

Box 25.1 Significant adverse effects of fever

- Increased insensible water loss
- Cardiopulmonary stress
- Paradoxical suppression of immune response
- Febrile seizures.

Table 25.1: Centigrade to Fahrenheit temperature reading

°C = °F	°C = °F	°C = °F	°C = °F
0 = 32	35.5 = 95.9	40 = 104	60 = 140
5 = 41	36 = 96.8	40.5 = 104.9	65 = 146
10 = 50	36.5 = 97.7	41 = 105.8	70 = 158
15 = 59	37 = 98.6	41.5 = 106.7	75 = 167
20 = 68	37.5 = 99.5	42 = 107.6	80 = 176
25 = 77	38 = 100.4	43 = 109.4	85 = 185
30 = 86	38.5 = 101.3	45 = 113	90 = 195
32 = 89.6	39 = 102.3	50 = 122	95 = 203
35 = 95	39.5 = 103.2	55 = 131	100 = 212

TYPES OF FEVER

■ **Short pyrexia:** The term denotes a fever of short duration, 1 or 2 days to 5 or 7 days. Most cases are secondary to acute infections like viral infections (coryza, common cold, malaria or urinary tract infection {UTI}).

■ **Prolonged pyrexia:** When fever extends beyond 7 days, it is customary to employ the term, **prolonged pyrexia**. In most cases, simple investigations contribute to arriving at the diagnosis. In some cases, this may not happen. The term, **pyrexia of unknown origin** is often used:

- When a child with prolonged fever of 2 weeks and outpatient department (OPD) investigations over 1 week remains undiagnosed as to the cause.
- When a child with prolonged fever of over 3 weeks and OPD investigations of 1 week remain undiagnosed as to the cause.

Nonviral conditions need to be seriously considered in such a case scenario.

■ **Fever without focus:** It is also termed as **fever without source**, it may be of two types:

1. Fever without localizing signs
2. FUO

FEVER WITHOUT LOCALIZING SIGNS

It is defined as a short duration fever of less than 1 week and a rectal temperature of 38°C or beyond without localizing signs. It is a diagnostic challenge in children less than 3 years of age, especially less than 3 months of age where chances of a serious bacterial infection are high.

The etiology as well as evaluation varies with the age group. Three high-risk age groups from etiologic and evaluation points of view are:

- Neonates
- Infants 1 month–3 months
- Infants 3 months–3 years.

Fever without Localizing Signs in Neonates

A febrile neonate stands a considerable chance (upto 15%) of having a serious infection and needs a thorough evaluation, preferably in hospital.

Having excluded dehydration, fever as a result of too much of clothing and/or high room temperature which needs replacement fluids and observations, the infant should be hospitalized especially when he is sick looking. Antibiotic therapy in keeping with policy of the nursery

should be instituted while waiting for the results of sepsis screen and other tests. If sepsis screen turns out to be negative, a repeat screen is done after 6-12 hours. If it is negative and the infant becomes afebrile, antibiotics may be withdrawn after 5 days. Else the infant should receive full course of antibiotic therapy as per norms.

Fever without Localizing Signs in Infants Aged 1–3 Months

Being an extension of neonatal period, serious bacterial infections continue to be significant though less (around 10% compared to 15% in first month of life).

If the infant is febrile without obvious cause such as upper respiratory infection (URI) but looks well, he should have sepsis screen plus peripheral film for malarial parasite, urine microscopy, urine and blood culture, chest X-ray, lumbar puncture (LP) depending on the merits of the situation. If all investigations are negative, he should be kept under observations. If the sepsis screen turns out to be positive, he should be treated on the lines of sepsis with appropriate antibiotics. If the febrile infant without localizing sign is sick-looking, he needs treatment just as in case of a sick neonate in a hospital.

Fever without Localizing Signs in Infants Aged 3 Months–3 Years

Serious bacterial infections being much less (5%), infections as a result of viruses are responsible for a vast majority of the infections in this age group.

As long as rectal temperature remains less than 39°C and the child is not toxic, he can be observed and followed up from home. In case temperature is more than 39°C and/or the child is toxic, he should be hospitalized and subjected to detailed evaluation and therapy in view of high risk of bacteremia. The first line tests include complete blood count (CBC) and blood film for malarial parasite. Total leukocytes count (TLC) ($<5000/\text{mm}^3$) points to a viral infection or enteric fever. TLC between 5000 and 15000/ mm^3 is a pointer for observations. In case TLC is $>15,000/\text{mm}^3$, blood culture needs to be sent.

If fever persists more than 48 hours without appearance of localizing signs, extended tests in the form of blood culture and urine microscopy for pus cells are indicated.

FEVER OF UNKNOWN ORIGIN (Pyrexia of Unknown Origin)

Definition

In the past, fever of unknown origin (FUO) has been variously defined by different experts. Currently, it is defined as a prolonged fever of three weeks or more duration without obvious cause on evaluation and simple investigations carried out at outpatient level or after one week of evaluation in the hospital.

Etiology (Table 25.2)

IN FUO too, infections continue to dominate the scene with over 60% cases being due to them. Important causative

Table 25.2: Etiology/differential diagnosis of FUO

Infectious diseases

- Enteric fever
- Malaria
- Tuberculosis
- UTI
- Infective endocarditis
- HIV/AIDS with opportunistic infection
- Viral hepatitis
- Liver abscess (occult)
- Kala-azar
- Rickettsial fever
- Spirochetal fever
- Brucellosis
- Leptospirosis.

Autoimmune disorders

- Juvenile rheumatoid arthritis
- SLE
- Kawasaki disease
- Rheumatic fever
- Polyarteritis nodosa
- IBD.

Malignancies

- Leukemias
- Lymphomas
- Wilms' tumor
- Neuroblastoma
- Pheochromocytoma
- Histiocytosis (Langerhas cell type).

Miscellaneous

- Drug fever
- Serum sickness
- Diabetes insipidus
- Chronic active hepatitis
- Sickle cell, crisis
- Ichthyosis.

Abbreviations: FUO, fever of unknown origin; UTI, urinary tract infection; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease.

infection in FUO are typhoid, UTI, malaria and tuberculosis. Nevertheless, as the illness becomes more prolonged, their incidence considerably falls down giving space to less common causes such as connective tissue/autoimmune disorders (say rheumatoid arthritis, systemic lupus erythematosus {SLE}, Kawasaki disease, etc.) followed by malignancies (say leukemias, lymphomas, etc.).

Occasionally, drug fever (with intense itching), diabetes insipidus, sensory autonomic neuropathies, etc. may be responsible for FUO.

Diagnostic Approach

At the outset, make sure that it is not a factitious fever. Diagnostic evaluation revolves around detailed history and physical examination followed by screening tests. With feedback from these, if the need be, further tests and imaging studies may be carried out (Box 25.2).

- **Clinical work-up:** A good history and physical examination are very important in evaluation of a FUO case (Box 25.2). The aim of the whole exercise is to find

Box 25.2 Framework of diagnostic and therapeutic approach to FUO

- History and physical examination
- Simultaneous stabilization
- Screening tests/first line tests
- Second line tests
- Treatment in keeping with the diagnosis.

Abbreviation: FUO, fever of unknown origin.

clues that may point to a specific infection or area of suspicion.

- **History:** It should elicit details about onset and other aspects of fever e.g. whether continuous, intermittent or remittent; whether tertian, quotidian or quartan; whether accompanied by chills and rigors; accompanying manifestations. Age of the patient needs consideration. Adolescents, in addition to other childhood conditions are more likely to have tuberculosis, inflammatory bowel disease (IBD), autoimmune disease or lymphoma. Likewise, likelihood of a respiratory, infection, genitourinary infection, abscess and osteomyelitis in more than 6 year olds is high.

History of pica may arouse suspicion of visceral larva migrans (*Toxocara canis*) and toxoplasmosis (*Toxoplasma gondii*). History of exposure to wild animals or pets may point to a zoonotic infection. History of use of medication such as atropine eye drops which may be responsible for atropine-induced fever.

- **Physical examination:** A detailed head to toe examination at the outset and every day is important to catch any emerging findings as a clue to the causative condition. Make a note of his overall general activity and nutritional status.
- **Sweating:** Persistent absence of sweating despite high fever should arouse suspicion of dehydration, nephrogenic diabetes insipidus, anhydrotic ectodermal dysplasia, familial dysautonomia and atropine-induced fever.
- **Eye findings:** A good ophthalmic examination may turn out to be revealing.
 - Petechial hemorrhages suggest infective endocarditis.
 - Uveitis points to juvenile rheumatoid arthritis, SLE, Kawasaki disease, Behcet disease and vasculitis.
 - Chorioretinitis may suggest toxoplasmosis, cytomegalovirus (CMV), rubella and syphilis.
 - Proptosis may mean orbital tumor, chloroma, thyrotoxicosis, neuroblastoma secondaries, orbital infection pseudotumor and Wegner's granulomatosis.
 - Failure of pupillary constriction may point to hypothalamic dysfunction as the cause of FUO.
 - Lack of tears with absent corneal reflex suggest familial dysautonomia.
- **Ear, nose and throat (ENT) findings:** Tenderness over sinuses or the upper teeth suggests sinusitis.
- **Oral cavity**
 - Recurrent oral candidiasis suggests immune system disorders.

- Fever blisters point to pneumococcal, streptococcal, malaria and rickettsial infections and sometime to salmonella and staphylococcal infections.

■ Muscle/bone tenderness

- **Generalized:** Kawasaki disease, dermatomyositis, polyarteritis, trichinosis, mycoplasma or arbovirus infection.
- **Point tenderness:** Occult osteomyelitis, bone marrow invasion from neoplastic disease.
- **Tenderness of trapezius:** Subdiaphragmatic abscess.
- **Rectal examination** may reveal per rectal adenopathy or deep pelvic abscess, iliac adenitis or pelvic osteomyelitis.
- **Occult blood** may point to ulcerative colitis or granulomatous colitis as the cause of FUO.
- **Hyperactive deep tendon reflexes** suggest thyrotoxicosis.
- **Chills and rigors** suggest sepsis, malaria, UTI, abscess, infective endocarditis, brucellosis, rat-bite fever.

FEVER WITH RASH

Whereas fever without a focus is a diagnostic dilemma, some children presenting for fever accompanied by rash may often pose a challenge.

Etiology

A large variety of rash occurs ranging in intensity from mild through moderate to severe. Moreover rash may be of varying types, say macular, maculopapular, urticarial, vesicular, petechial or purpuric, nodular, etc. (Table 25.3).

Diagnostic Approach

- **History:** A good history with information on nature, severity and distribution of rash assists in of the case presenting with fever and rash. The diagnosis also helpful information is intake of a drug, involvement of mucosal sites, distribution of rash, immunization status, etc. Presence of intense itching usually favors a drug rash than an exanthemata.
- **Physical examination:** Complete physical check-up with special reference to intensity (severity), nature and distribution (Box 25.3) and severity of rash. Associated findings such as hepatosplenomegaly, lymphadenopathy and meningeal involvement should also be taken into consideration (Box 25.4).

Laboratory Tests

- Complete blood picture (CBP) should be done in every case.
- Depending on the individual merits of the cases:
 - C-reactive protein (CRP)
 - Erythrocyte sedimentation rate (ESR)
 - Blood culture
 - Serology (e.g dengue)
 - Biopsy may be considered.

Table 25.3: Variety of rash and causative conditions

Nature of rash	Usual causative condition	Uncommon causative conditions
Macular/maculopapular rash	Measles, rubella, <i>Roseola infantum</i> , erythema infectiosum, dengue, adenoviral infections, enteroviral infections; drug hypersensitivity	Infectious mononucleosis, CMV, HIV/AIDS, chikungunya, chronic hepatitis B, <i>Mycolasma pneumoniae</i> infection, syphilis (secondary), brucellosis, JIA (systemic-onset) and scrub typhus
Vesicular rash	Varicella (chickenpox), hand-foot-mouth disease (enteroviral infection)	Herpes (both simplex and zoster), papulonecrotic tuberculosis
Pleomorphic rash (vesicles, pustules, crusts)	Varicella	
Urticarial rash	Insect bite, drug rash and scabies	Louse infestation (pediculosis), hookworm and strongyloides infestations causing cutaneous larva migrans
Diffuse erythema with desquamation of skin	Stevens-Johnson syndrome, Kawasaki disease, toxic epidermolysis (drug-induced)	Toxic shock syndrome, (both <i>Staphylococcal</i> and <i>Streptococcal</i>), β -hemolyticus (GAS) infection (Scarlet fever)
Nodular rash	Tuberculosis (erythema nodosum), molluscum contagiosum, IBD both Crohn and ulcerative colitis, drugs, leprosy (lepromatous) and sarcoidosis	Histoplasmosis (disseminated) and cryptococcosis.

Abbreviations: IBD, inflammatory bowel disease; GAS, group A streptococcus; CMV, cytomegalovirus; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; JIA, juvenile idiopathic arthritis.

Box 25.3 Significance of distribution of rash**Centripetal**

Varicella

Over Palms and soles

- Kawasaki disease
- Stevens-Johnson syndrome
- Hand-foot-mouth disease
- Dengue
- Spotted fever.

Box 25.4 Significance of associated findings**Mucous membrane involvement**

Measles (Koplik spots)

Meningeal involvement

Meningococcal meningitis

Organomegaly (Hepatosplenomegaly)

Typhoid

Lymphadenopathy

Infectious mononucleosis, Kawasaki disease

Shock with acute kidney injury (AKI)

Meningococemia.

- Malaria parasite
- Urinalysis and culture
- CRP
- Blood culture
- Widal test
- Mantoux test
- Liver function test (LFT)
- Chest X-ray
- Abdominal ultrasound.

■ **Second line investigations:**

- Human immunodeficiency virus (HIV)/enzyme linked immunosorbent assay (ELISA)
- Computed tomography (CT) scan of chest and abdomen
- Bone marrow: smear, biopsy and culture
- Complement C₃ level
- Antinuclear antibody
- Rheumatoid factor
- Specific tissue biopsies
- Other tests—serology for brucellosis, Paul Bunnell test, hepatitis B surface antigen (HBsAg), Monospot test, IgM antibody to viral capsid antigen for infectious mononucleosis.

Management

- After the initial evaluation and while the investigations are in progress, the child suffering from fever with rash needs observations and supportive care.
- Once the diagnosis is reached, treatment no longer remains a problem. Unnecessary delay in treatment should not be there.
- In the event of an occasional child in whom diagnosis remains elusive in spite of good work-up, symptomatic and supportive treatment should be instituted.
- If a drug seems to be the offending agent in causation of fever with rash, it should be withdrawn and the child observed for response to such a withdrawal.

INVESTIGATIONS■ **First line (screening) investigations:**

- CBP
- ESR

MANAGEMENT

Once, after due evaluation, cause of FUO is clear, treatment should pose no problem. Use of antibiotics should be rational rather than empirical, except in an occasional situation when clinical indication overweighs the doubtful laboratory findings. Use of antipyretics (preferably paracetamol, ibuprofen) may be in place to provide symptomatic relief.

PROGNOSIS

In most cases, usually having unusual presentation of a common disease as cause of FUO, a precise diagnosis is reached and problem is resolved following treatment. In a proportion, no diagnosis is reached. Most of them settle on their own with fever abating spontaneously. Occasionally, cause remains undetermined and fever too persists.

Multiple Choice Questions

- Spot the wrong observation:
 - The cutoff point for fever is a rectal temperature of 38°C or 100°F
 - The so-called "heat illness" is not a true fever
 - Presence of erythema nodosum invariably suggests the diagnosis of histoplasmosis or cryptococcosis
 - Pleomorphic rash strongly suggests diagnosis of chickenpox
- Significant adverse effects of fever include all, except:
 - Cardiopulmonary stress and paradoxical suppression of immune system
 - Febrile seizures
 - Dehydration from insensible losses
 - Diarrhea
- All of the following statements about fever of unknown origin are true, except:
 - Over 60% cases are because of infections
 - Drug fever, diabetes insipidus and sensory autonomic neuropathies figure among the infrequent causes
 - Presence of associated uveitis is pathognomonic of inflammatory bowel disease
 - Lack of tears with absent corneal reflex suggest familial dysautonomia
- A 14-month-child with fever, coryza, cough and conjunctivitis develops a maculopapular rash on 5th day of illness. What is the most probable cause?
 - Chickenpox
 - Measles
 - Scarlet fever
 - Roseola infantum
- Persistent absence of sweating despite high fever should arouse suspicion of:
 - Dehydration
 - Nephrogenic diabetes insipidus
 - Atropine-induced fever
 - All of the above
- Pick up wrong matching in a case of fever:

A. Tenderness of trapezius	Subdiaphragmatic abscess
B. Fever blisters	Tuberculosis
C. Hyperactive deep tendon reflexes	Thyrotoxicosis
D. Lack of tears plus absent corneal reflex	Familial dysautonomia

Answers

1. C 2. D 3. C 4. B 5. D 6. B

Clinical Problem-solving

Review 1

A 6-year-old girl presents with prolonged fever of over a month's duration. A few days later, she develops cough and complains of fatigue and generalized weakness. In addition, she shows significant cervical, axillary and inguinal lymphadenopathy, moderate anemia and grade 2 malnutrition. Her father died of a chronic respiratory illness a year back.

- What is the probable diagnosis?
- How will you confirm the projected diagnosis?
- What's the currently recommended specific treatment in India?

Review 2

A 12-year-old well built boy (height 151 cm, weight 35 kg) presents with 8 weeks history of fever with progressive pallor, generalized lymphadenopathy and breathlessness (grade 3 dyspnea). Chest X-ray shows massive widening of the superior mediastinum.

- Your diagnosis
- How can the diagnosis be confirmed?
- What is the prognosis?

Answers

Review 1

- Tuberculosis.
- Tuberculin test, FNAC/lymph node biopsy, CXR, sputum examination for AFB.

contd...

3. The consensus recommendation of the Revised National Tuberculosis Control Program (RNTCP) is 4 drugs INH, rifampicin, pyrazinamide and ethambutol for 2 months followed by withdrawal of pyrazinamide and continuation of rest of the 3 drugs for a full course of 6 months.

Review 2

1. Non-Hodgkin lymphoma, most probably lymphoblastic type, with superior vena cava syndrome.
2. Histology on lymph node biopsy is the best means of diagnosis.
3. Chemotherapy on the lines of acute lymphoblastic leukemia (ALL) has considerably improved the survival. The present case also needs radiotherapy in the wake of superior vena caval syndrome.

FURTHER READING

JOURNAL ARTICLES/CHAPTERS

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BOOK/MONOGRAPH

1. Montgomery S. *Pediatric Fever: A Friend or a Foe*. London: Smithsons 2013.

SECTION 5

Pediatric Subspecialties

Section Outline

26. Pediatric Pulmonology
27. Pediatric Cardiology
28. Pediatric Neurology
29. Pediatric Gastroenterology
30. Pediatric Hepatology and Pancreatology
31. Pediatric Nephrology
32. Pediatric Hematology
33. Pediatric Oncology
34. Pediatric Immunology
35. Pediatric Rheumatology
36. Pediatric Dermatology
37. Accidental Poisoning
38. Envenomation
39. Pediatric Endocrinology
40. Genetics in Health and Disease
41. Inborn Errors of Metabolism
42. Neuromuscular Disorders

INTRODUCTION

Diseases pertaining to the respiratory system are responsible for a large proportion of pediatric admissions and outpatient attendance. In India, the highest incidence is recorded in the winter followed by the relatively lower peak during rainy season.

Like in other tropical areas, Indian infants and children demonstrate pattern of clinical presentation which is somewhat different from what is recorded by the western authorities. This variance is related to factors, such as considerable delay in reporting to the hospital and high frequency of infestations and associated malnutrition. All these, individually or collectively, result in a rather somewhat changed clinical picture.

CLINICAL EVALUATION OF A RESPIRATORY CASE

For role of history-taking and clinical examination in evaluation of a respiratory case, See Chapter 2 (Pediatric History-taking and Physical Clinical Examination).

SPECIAL DIAGNOSTIC PROCEDURES

Radiology/Imaging

- **Chest X-ray:** Posteroanterior (PA) and lateral views as a routine, decubitus film for pleural effusion, oblique film for focus on hilar shadow and lung portion at the back of heart, lordotic film for apices, lateral neck film for upper airway obstruction round the level of retropharynx, subglottis and supraglottis.
- **Barium swallow:** It is useful in excluding tracheoesophageal fistula (TEF) of H-type, gastroesophageal reflux disease (GERD) and esophageal indentation with vascular rings.
- Screening (fluoroscopy) is of value for stridor and movements of diaphragm and mediastinum.
- Ultrasonography is useful in pleural effusion, lobar pneumonias and intrathoracic masses as also in guiding conduction of lung tap and pleural tap.
- Computed tomography (CT) scan is very helpful in pleural, mediastinal, and parenchymal (both solid and cystic) lesions, bronchiectasis, vascular structures (provided that IV contrast enhancer is employed), and guiding biopsy.
- Magnetic resonance imaging (MRI) is particularly of great value in vascular rings and hilar structures.

Table 26.1: Indications of microbiologic examination of body secretions in the diagnosis of respiratory diseases

Secretions	Indications
Sputum, tracheal, bronchial, gastric microscopy/culture	Lung abscess, bronchiectasis, cystic fibrosis, tuberculosis, <i>Pneumocystis carinii</i> , <i>Pneumonia</i>
Nasal cytology for eosinophils	Allergic rhinitis, nasobronchial allergy
Special iron stains of bronchial secretions	Hemosiderosis

Serology

Immunoglobulins (IgG, IgA, IgM, IgD and IgE), eosinophilic cationic protein levels are elevated in asthma. Antibodies to cytomegalovirus (CMV), respiratory syncytial virus (RSV), chlamydia and mycoplasma can be detected.

MICROBIOLOGIC EXAMINATION OF BODY SECRETIONS

Sputum, nasal cytology, tracheal secretions, throat swab, bronchial aspiration, gastric lavage, etc. can be microscopically examined, at times following special stain like Ziehl-Neelsen stain for acid-fast bacillus (AFB) and even cultured for exact microbial growth and antibiotic sensitivity in several conditions (Table 26.1).

Skin Tests

These include Mantoux test (sometimes Bacillus Calmette-Guérin {BCG} diagnostic test) for tuberculosis, Kveim test for sarcoidosis, Casoni test for hydatid disease and skin tests (patch-prick and intradermal tests) for allergens.

PILOCARPINE IONTOPHORESIS FOR SWEAT CHLORIDE

A sweat chloride level of more than 60 mEq/L in a child with clinical profile of cystic fibrosis establishes the diagnosis. For quick molecular diagnosis of cystic fibrosis (CF), especially for research purposes, polymerase chain reaction (PCR) and deoxyribonucleic acid (DNA) studies are now available.

Pulmonary Function Tests

Pulmonary function tests include:

- Spirometry (the most important) measures forced vital capacity (FVC), forced expiratory volume (FEV1)

Table 26.2: Arterial blood gas levels

Criteria	Normal blood level	Blood level in acute respiratory failure
pH	7.35–7.45	
PCO ₂	35–45 mmHg	>50 mmHg
PO ₂	90 mmHg	<60 mmHg

in 1 second, FEV1/FVC ratio, maximal midflow (MMF) between 25% and 75% of FVC or, alternatively, forced expiratory flow (FEF) between 25% and 75% of FVC.

- Mini Wright peak flow meter for evaluation of obstruction and response to bronchodilator therapy.
- Bronchial provocation using methacholine and histamine.

Arterial Blood Gas Analysis

Arterial oxygen and carbon dioxide levels faithfully reflect the state of ventilation, perfusion and gas exchange. Table 26.2 gives the normal levels.

Transillumination

This is a useful simple maneuver to diagnose pneumothorax in an infant under 6 months of age. A large halo of light is seen around the fiber optic light scope.

DIRECT LARYNGOSCOPY

This is usually carried out using a fiber optic or rigid scope under general anesthesia or sedation in the evaluation of an upper airway obstruction or stridor.

Bronchoscopy

The procedure is carried out under general anesthesia employing a fiber optic or rigid bronchoscope in the following situations:

- Foreign body
- Intractable wheeze
- Recurrent or persistent pneumonia
- Atelectasis

- Immunocompromised state with unexplained interstitial pneumonia
- Hemoptysis
- Lung mass causing pressure symptoms.
Bronchoscopy may serve both a diagnostic and therapeutic purpose.

Thoracoscopy

Thoracoscopy is a useful procedure for evaluating the pleural cavity. The instrument used (thoracoscope) is similar to a bronchoscope.

Thoracocentesis

Intercostal drainage is indicated for obtaining pleural fluid sample for diagnostic purpose and in case of a massive pleural effusion causing dyspnea. It is best done in the 5th–7th intercostal space on the posterior axillary line.

Lung Tap

It is needed for obtaining specimen of the pulmonary parenchyma and is done with a needle subsequent to installation of saline.

Lung Biopsy

This procedure is indicated for diagnosis of *pneumocystis carinii* and other diffuse lung diseases and may be done either by open surgery or via a bronchoscope or endotracheal tube.

Polygraphic Monitoring

This consists in monitoring of heart rate, electrocardiogram (ECG), movements of chest and abdomen, arterial partial pressure of carbon dioxide (PCO₂) and arterial blood (SaO₂) in cases of obstructive apnea and upper airway obstruction.

RESPIRATORY MANIFESTATIONS OF SYSTEMIC DISEASE

Respiratory system is a common site of secondary involvement in several systemic disorders and diseases of organs (Box 26.1).

Box 26.1 Respiratory manifestations of systemic diseases

GIT disorders

- **GERD:** Chronic cough, raspy voice, sore throat, recurrent pneumonia, wheezing (even asthma)
- **Hepatopulmonary syndrome:** Hypoxemia, cyanosis, clubbing

Pancreatic disorders

- **Acute pancreatitis:** Acute respiratory insufficiency, pleural effusion
- **Cystic fibrosis:** RRI

Hematological disorders

- **Anemias:** Hypoxemia, dyspnea
- **Sickle-cell disease:** Sickle crisis (pneumonia-like illness characterized by fever, tachypnea, chest pain, dyspnea, hypoxemia and fatigue), acute chest syndrome (fever, dyspnea, chest pain, CXR showing patchy shadowing of a lobe; later pleural effusion causing total 'whiteout' in CXR)
- **Lymphomas:** Respiratory distress from mediastinal lymphadenopathy
- **Leukemia:** Pulmonary infiltrates and nodules
- **Multiple myeloma:** Lytic lesions in thoracic cage

Congenital heart disease

- **Left-to-right shunt:** Recurrent respiratory infection
- **Cardiomyopathy:** Airway compression

contd...

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- **Vascular anomalies:** Airway compression
- **Congestive cardiac failure:** Left-sided—tachypnea, right-sided—pulmonary edema
- **Postsurgical repair:** Restrictive lung function

Neurological disorders

- **CNS infections (meningitis, encephalitis):** Cheyne-Stokes breathing (periods of hyperventilation alternating with apnea)
- **GBS:** Respiratory failure from paralysis of involved muscles
- **Neurofibromatosis:** Interstitial pulmonary fibrosis, obstructive sleep apnea
- **Tuberous sclerosis:** Pulmonary lymphangioleiomyomatosis (overgrowth of smooth muscle cells in pulmonary lymphatics, blood vessels and airways causing small airway obstruction, cyst formation, pneumothorax, chylothorax, hemoptysis)

Vasculitis

- **Wegener granulomatosis:** Upper and lower respiratory tract involvement
- **Churg-Strauss syndrome:** Asthma, pleural effusion, eosinophilic infiltrations, diffuse alveolar hemorrhage
- **Henoch-Schönlein purpura:** Diffuse alveolitis causing alveolar hemorrhage, hemoptysis, pulmonary infarcts
- **Behcet's disease:** Cough, fever, hemoptysis, pleuritis, rupture of aneurysm of outlet pulmonary artery, pulmonary hypertension. Takayasu arteritis (pulseless disease); pulmonary artery thrombosis, stenosis and poststenotic dilatation
- **Goodpasture syndrome:** Dry cough, slight dyspnea; in severe cases, hemoptysis from pulmonary hemorrhage

Connective tissue disorders

- **Juvenile rheumatoid arthritis:** Pleural effusion, diffuse rheumatoid lung disease, eosinophilic pneumonia, bronchiolitis obliterans organizing pneumonia (BOOP), shrinking lungs, upper lobe fibrosis with cavitation; enhanced vulnerability for bronchiectasis, tuberculosis, empyema
- **Systemic lupus erythematosus:** Pulmonary hemorrhage, infarction, embolism, infiltrates and chronic fibrosis; pleuritis, shrinking lungs manifesting with moderate to severe dyspnea and paradoxical abdominal movements with respiration
- **Sjögren syndrome:** Desiccation of trachea and bronchial tree resulting in recurrent respiratory infection, airflow limitation, bronchiectasis, fibrosis alveolitis, lymphoid interstitial lung disease, hypergammaglobulinemia, etc.
- **Juvenile dermatomyositis:** Dysphonia, aspiration pneumonia, respiratory muscle weakness, pneumothorax
- **Scleroderma:** Interstitial lung disease
- **Ankylosing spondylitis:** Chest wall restriction (secondary to fusion of costovertebral joints) causing predisposition to respiratory infection, impaired lung function, upper lobe fibrotic disease, etc.
- **Amyloidosis:** Tracheobronchial involvement causing dyspnea, cough and hemoptysis, respiratory failure
- **Sarcoidosis:** Cough, dyspnea, chest pain, hemoptysis, airway obstruction and bronchiectasis; airway hyper-reactivity

Dyselectrolytemia

- **Metabolic acidosis:** Kussmaul breathing (hyperpnea) manifesting as deep, rapid respiration (compensatory mechanism to compensate for acidosis).
- Respiratory acidosis
- Respiratory alkalosis

Immunodeficiency

- **HIV/AIDS:** Recurrent URTI, infections with opportunistic pathogens, lymphoid interstitial pneumonia, *Pneumocystis carinii** pneumonia (PCP).
- One-half of HIV/AIDS subjects suffer from respiratory illnesses.

Abbreviations: GIT, gastrointestinal; GERD, gastroesophageal reflux disease; RRI, recurrent respiratory infections; CXR, chest X-ray; CNS, central nervous system; URTI, upper respiratory tract infection; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

New name *Pneumocystis Jiroveci*. Rather than a Protozoan, now it is considered a fungus.

COMMON MANIFESTATIONS OF RESPIRATORY DISEASE

Cough

Definition

Cough, a defense and alert manifestation and the most common symptom of respiratory disease, is defined as an explosive and noisy bout of expiration aimed at expelling the unwanted secretions and/or foreign material from the tracheobronchial tree. It may be mild or severe, dry or with expectoration, and acute or chronic/persistent. It can be voluntary as well as involuntary or reflex.

Etiology

It can take origin from pharynx, larynx, trachea, bronchi, bronchioles and parenchyma as a consequence of stimulation of sensory nerves in their mucosa.

Exogenous irritants include foreign bodies, smoke, fumes and dust. **Endogenous factors** include both upper

Box 26.2 Causes of cough

- **Newborn:** Birth—TEF (H type), laryngeal webs, vascular rings, rest of neonatal period—Interstitial pneumonia from torch infections
- **Infancy:** Early—GER, later—pertussis, bronchiolitis, asthma, CF
- **Preschool age:** Postnasal drip, asthma, bronchitis (both infective and allergic), tropical eosinophilia, foreign body, psychogenic cough, habit cough
- **Miscellaneous (any age):** Asthma, pertussis, tuberculosis, foreign body, bronchitis.

Abbreviations: TEF, tracheoesophageal fistula; CF, cystic fibrosis; GER, gastroesophageal reflux.

and lower airway inflammation, GERD, asthma, compression, allergy, etc. Causes in relation to age group are listed in Box 26.2.

Diagnostic Evaluation

Chronic cough can be a diagnostic challenge, though most cases with normal chest X-ray can be explained by postnasal drip due to nasal or sinus disease, GERD or asthma.

428 Treatment

It depends on the cause, e.g. asthma, pertussis, CF, etc. For symptomatic relief in severe cough, a safe cough suppressant (dextromethorphan) may be used for a limited period in dry cough.

Wheezing

Definition

Wheezing is defined as the high-pitched whistling sounds, often heard from a distance without the aid of the stethoscope, from partial obstruction of the bronchi and the bronchioles. Predominantly, these are expiratory.

Etiopathogenesis

Partial obstruction of air passages (bronchi and bronchioles) due to causes in the lumen, in the wall or outside the wall, is responsible for producing wheezing. Conditions manifesting with wheezing are listed in Box 26.3.

Differential Diagnosis

Wheezing should not be confused with the following respiratory sounds:

- **Stridor:** Usually an inspiratory sound secondary to upper airway obstruction (usually in larynx or trachea) of irregular quality produced by oropharyngeal obstruction. Expiratory stridor is infrequent.
- **Grunting:** Expiratory sound produced by partial closure of glottis. Classically, it is encountered in respiratory distress syndrome (hyaline membrane disease).
- **Snoring:** It is a low-pitched inspiratory sound usually originating from oropharynx.
- **Rattling:** Coarse inspiratory sounds which are felt as vibrations when head is placed over the chest as a result of some obstruction in larynx or trachea.

Treatment

Treatment is dictated by the etiological condition. Bronchodilators provide relief by decreasing the bronchospasm.

Box 26.3 Conditions producing wheezing

- Wheezy, spasmodic or asthmatic bronchitis*
- Bronchial asthma
- Bronchiolitis
- Tropical eosinophilia
- Loeffler syndrome and other hypereosinophilic states
- Mediastinal glands, tumors or aberrant vessels compressing the trachea or bronchi
- Cystic fibrosis
- Foreign body
- Pulmonary hemosiderosis
- **Aspiration syndromes:** Prematurity, hiatal hernia, tracheoesophageal fistula, chalasias of esophagus, epilepsy, kerosene, paraffin, baby powder
- Congestive cardiac failure
- Gastrointestinal reflux
- Immunodeficiency states
- Bronchiectasis, postpertussis, Kartagener syndrome.

*Usually, potential asthma cases, needing evaluation and follow-up.

Box 26.4 Causes of stridor

- **Congenital:** Pierre Robin syndrome, laryngomalacia, laryngeal web, stenosis, papilloma, vascular ring, tracheoesophageal fistula, cystic hygroma, retrosternal goiter
- **Infection:** Laryngitis, epiglottitis, laryngotracheobronchitis, diphtheria, peritonsillar or retropharyngeal abscess
- **Trauma:** Intubation, inhalation burn.
- **Mechanical:** Foreign body, enlarged tonsils and adenoids, cysts or tumors of vocal cord, goiter
- **Vocal cord paralysis:** Local—birth trauma, patent ductus arteriosus (PDA)
Central—cerebral palsy, hydrocephalus
- **Nutritional:** Tetany
- **Allergic:** Angioneurotic edema.

Stridor

Definition

The term denotes noisy breathing resulting from obstruction to the free flow of air through the larynx or trachea.

- In supraglottic stridor, the noise is inspiratory and characterized by a low-pitched flutter. Voice may remain normal.
- In glottic stridor, noise is inspiratory and expiratory, exhibiting a phonatory quality. Dyspnea is present.
- In subglottic stridor, noise is mainly expiratory. Brassy, barking cough is characteristic. Voice may remain normal.

Etiology

It is summarized in Box 26.4. In an overwhelming majority (75%) of infants with stridor, the cause is laryngomalacia (*vide infra*).

Laryngomalacia refers to congenital thickness and flabbiness of structures surrounding the laryngeal aperture, particularly the aryepiglottic folds. During inspiration, they collapse into the laryngeal inlet, causing narrowing and inspiratory noise. It manifests as inspiratory stridor within a few weeks of birth. The stridor becomes more pronounced on crying or when the infant lies supine (i.e. on his back). Direct laryngoscopy shows indrawing of the aryepiglottic folds. When laryngoscopy is passed in between these folds, stridor disappears.

Treatment

Treatment revolves around reassurance. It gradually decreases in severity, usually subsiding by 6–12 months age. Often it may persist for 2–3 years. Figure 26.1 focuses on the sites of development of stridor vis-à-vis wheeze.

Dyspnea

(Respiratory Distress, Breathlessness)

The term **dyspnea**, denotes difficult/labored respiration. Some pain and hunger are usually associated with it. The term **tachypnea** refers to abnormally increased respiratory rate. Severity of dyspnea is graded as per Box 2 in Chapter 2 (Pediatric History-taking and Physical {Clinical} Examination). Etiology varies in various age-groups. Both pulmonary and extrapulmonary conditions (especially

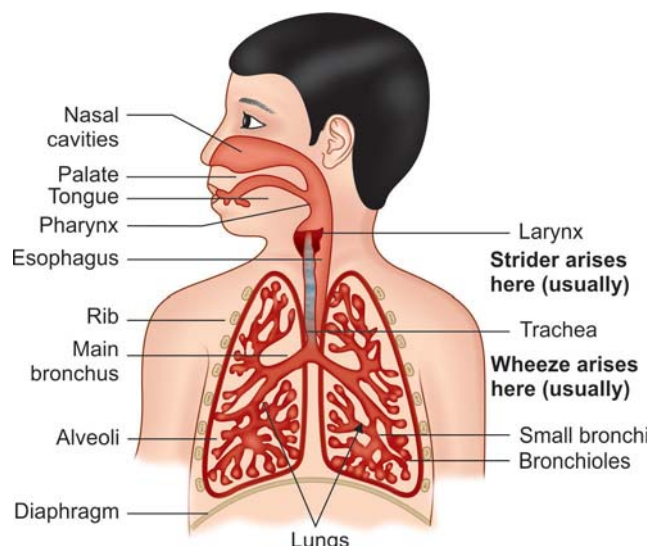


Fig. 26.1: Sites of development of stridor vis-à-vis wheeze.

congenital and acquired heart disease). More details are available in relevant etiological conditions discussed elsewhere.

Epistaxis

(Nosebleeds)

Nosebleeds are common after first year and upto puberty. About 10% of children suffer from this symptom, a vast majority of the bleeds being minor and transient, stopping spontaneously or with little pressure.

Location of epistaxis usually is the anteroinferior part of the cartilaginous nasal septum with rich blood supply, termed Kiesselbach plexus, (area or triangle) (Fig. 26.2) followed by mucosa lining the anterior portion of the turbinates.

Etiology

Etiologic factors include trauma (nose picking being the most common cause of epistaxis in childhood), upper respiratory infection/allergy, physical and emotional stress and strain (forceful cough, sneezing, exertion, excitement), foreign body, solar radiation, polyp, congenital vascular



Fig. 26.2: Epistaxis. Note the Kiesselbach's plexus.

defects (telangiectasias, varicosities), systemic disease (hypertension, uremia, cirrhosis, nephritis, rheumatic fever, enteric fever) and bleeding disorders (leukemias, purpuras, disseminated intravascular coagulation {DIC}).

Tuberculosis, syphilis, leprosy, fungal infections, tumors, puberty (menarche), high altitude, scurvy, vitamin K deficiency, sickle-cell disease, brucellosis, etc. may also be accompanied by nosebleeds.

Treatment

Isolated episodes of nosebleeds, especially when minor and restricted to the anterior nares, do not need any diagnostic evaluation. For severe and repeated episodes originating from posterior nares, especially in association with bleeding from other sites, a complete ear, nose and throat (ENT) and hematologic workup is indicated to find out the primary cause of bleeding.

- First aid measure for stopping bleeding consists in compressing the nares with two fingers with the head tilted forward.
- If the above maneuver fails, local application of epinephrine, 1 in 1,000 solution, preferably with thrombin, is indicated.
- Nasal packing (anterior, or combined anterior and posterior) may be needed in some cases.
- Cauterization with silver nitrate of the bleeding site to prevent further bleeding may be done after the bleeding has stopped.
- Blood transfusion may be indicated in certain subjects with severe or recurrent epistaxis.

Hemoptysis

True blood in sputum is an infrequent manifestation in children. Care should be exercised in differentiating it from blood tinges in saliva secondary to lesions of the buccal mucosa. Causative conditions include:

- Foreign body aspiration
- Bleeding disorder
- Necrotizing pneumonia
- Pulmonary tuberculosis (cavitary)
- Goodpasture syndrome
- Mitral stenosis
- Cardiomyopathy.

In an established case of hemoptysis, clinical and investigative evaluation, complete blood picture (CBP), chest X-ray (CXR) is critical to arrive at the diagnosis. Treatment depends on the diagnosis.

UPPER RESPIRATORY TRACT INFECTION

(Upper Respiratory Catarrh; Common Cold; Rhinopharyngitis, Acute Nasopharyngitis)

Definition

Upper respiratory tract infection (URTI) is defined as an inflammation of the upper respiratory tract, resulting in nasal discharge which is only watery or mucoid in majority

430 of the cases. It is a very common ailment of children, usually viral in etiology and droplet mode of spread.

Etiology

URTI is usually caused by over 150 serologically different viruses, the major share being of the rhinoviruses, all of which belong to picornavirus family of small ribonucleic acid (RNA) viruses.

Among bacteria, group A streptococci (GAS) take the lead through *Mycoplasma pneumonia*, *Corynebacterium diphtheriae*, *Neisseria meningitidis* and *Neisseria gonorrhoeae* may also cause URTI. *Hemophilus influenzae*, *Pneumococcus* and *Staphylococcus aureus* are responsible for superimposed infection, leading to complications related to ears, sinuses, mastoids, lymph nodes and lungs. Symptoms of asthma may get precipitated or aggravated in a child with reactive airway.

Clinical Features

Mild cases have just rhinorrhea, slight fever and irritability. Moderate catarrh is characterized by purulent nasal discharge, dry cough with postnasal discharge, fever, malaise, anorexia, etc.

Severe URTI is characterized by coexisting adenitis, tonsillitis, pharyngitis and extension of the infection to ears and lower down to larynx and bronchi. Ingestion of infected secretions may cause diarrhea and abdominal pain.

Complications

These include:

- Otitis media
- Sinusitis
- Lower respiratory tract infection (LRTI)—laryngitis, bronchiolitis, bronchopneumonia
- Asthma exacerbation.

Treatment

- **Mild URTI:** These cases of mild catarrh do not need anything beyond local decongestants, like saline nasal drops (xylometazoline or ephedrine nasal drops should be reserved for nonresponders and given for a day or two to safeguard against rebound) which are best administered while the child is lying supine with the neck slightly hyperextended.
- **Moderate URTI:** Treatment of moderate catarrh is more or less symptomatic. In addition to decongestants, antipyretics may be needed. Cough mixtures are best avoided.
- **Severe URTI:** An antibiotic, like penicillin, ampicillin, amoxicillin or erythromycin may be used if nasal discharge becomes purulent, fever fails to subside, likelihood of complications and an assumption of a superimposed bacterial infection.

SINUSITIS

Frontal sinus begins to grow after birth as nasofrontal ducts whereas maxillary, ethmoidal and sphenoidal sinuses are

present right at birth. As the primary and secondary teeth move towards alveolar margin, maxillary sinuses grow into the body of maxilla. After 6th year, floor of antrum lies at the level of the floor of nasal cavity.

Acute purulent sinusitis may occur either secondary to acute rhinitis or as an acute empyema. *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Hemophilus influenzae* are the usual etiologic agents.

Clinical Features

Manifestations include severe or prolonged cold, pyrexia, headache, facial pain, daytime cough and tenderness over the sinuses. Postnatal discharge may cause sore throat or a persistent cough at night. Periorbital cellulitis points to involvement of ethmoid sinuses. Complications include periorbital or orbital cellulitis, cavernous sinus thrombosis, meningitis, optic neuritis, subdural abscess and osteomyelitis.

Diagnosis is by demonstration of air-fluid levels and complete opacification and a mucosal width of 4 mm or more on X-ray/CT scan.

Treatment

Treatment is with an effective antibiotic therapy (amoxicillin as such or in combination with potassium clavulanate in case of beta-lactamase producing organisms, cephalosporins, cotrimoxazole, erythromycin, etc.).

Chronic Sinusitis

It suggests existence of a predisposing disorder, such as DNS, polyps, adenoids, septic tooth, allergy, cystic fibrosis, dyskinetic cilia or an immunodeficiency state. Alpha-hemolytic streptococci, *Staphylococcus aureus* and anaerobes plus the organisms responsible for acute sinusitis are the causative agents. Manifestations include persistent or recurrent attacks of nasal and postnasal discharge, low-grade fever, malaise, anorexia and easy fatigability. When it occurs in association with lower respiratory tract disease, the term **sinus bronchitis**, may be employed. All complications of acute sinusitis may also occur in chronic sinusitis.

Radiography, especially a lateral view of the nasopharynx, should always be done in suspected sinusitis. An opacity from sinusitis is far more dense than that seen in restricted air entry into sinuses due to swelling of nasal mucous membrane. A fluid level in a sinus is diagnostic. In the presence of radiographic evidence of sinus disease, aspiration proof puncture is performed. If mucus is obtained, it should be sent for culture and sensitivity.

Treatment is directed at administering suitable antibiotics for upto 6 weeks plus nasal drops of oxymetazoline HCl (0.05%, 0.025%) which are best administered by laying the child flat on his back with his head hanging over the side. Radical sinus surgery is usually not required in children.

ACUTE PHARYNGITIS

(Acute Pharyngotonsillitis, Acute Tonsillopharyngitis, Acute Tonsillitis, Sore Throat)

The term applies to conditions in which principal involvement is of throat. Tonsillitis and pharyngotonsillitis are covered under this caption. It usually occurs after first year of life.

Etiology

Viruses and group A beta-hemolytic streptococci are responsible for virtually all cases of acute pharyngitis.

Clinical Features

- **Viral pharyngitis** is characterized by fever, malaise and anorexia followed in a day or so by sore throat, hoarseness, cough and rhinitis. Throat examination reveals slight to intense inflammation with exudates and small ulcers over posterior pharyngeal wall, tonsils, soft palate and lymphoid follicles of palate. Lymphadenopathy and laryngeal involvement are common.
- **Streptococcal pharyngitis** is characterized by complaints such as headache, vomiting, abdominal discomfort and fever followed within hours by intense sore throat and mild to severe dysphagia. Throat examination shows diffuse congestion of the tonsils and its pillars with petechiae over the soft palate. Anterior cervical lymphadenopathy is common.

Diagnosis

Clinical diagnosis may be confirmed by culture of the throat swab or by rapid detection method for streptococcal antigens.

Differential Diagnosis

It is from diphtheria, infectious mononucleosis, herpangina (caused by group A coxsackie virus), agranulocytosis, tobacco and marijuana smoking, allergic rhinitis with postnasal drip, gonococcal pharyngitis and pharyngoconjunctival fever.

Complications

Viral pharyngitis may cause several complications (Box 26.5).

Treatment

- **Specific:** Streptococcal pharyngitis shows dramatic response to penicillin (oral, i.e. penicillin is good enough), erythromycin, amoxicillin, or cephalexin for 10–14 days. Once daily amoxycillin therapy has been found to be quite effective in group A beta-hemolytic streptococcal pharyngitis. A short 3–5 days' course of azithromycin too yields gratifying results.
- **Symptomatic:** Symptomatic measures include analgesics/antipyretics/anti-inflammatory agents, bed-rest as far as possible, warm saline gargles, steam inhalation,

Box 26.5 Complications of pharyngitis

Viral pharyngitis

- Purulent bacterial otitis media
- Large chronic ulcers in the pharynx in debilitated children
- Mesenteric adenitis

Streptococcal pharyngitis

- Large chronic ulcers in the throat
- Sinusitis
- Otitis media
- Chronic ulcers in the pharynx
- Acute glomerulonephritis
- Rheumatic fever
- Meningitis
- Mesenteric adenitis.

etc. A carrier state is an indication for another course of penicillin plus rifampicin 20 mg/kg once daily for 4 days towards the end of the penicillin course. Antibiotic prophylaxis against streptococcal disease is indicated in only a small proportion of cases.

CHRONIC TONSILLITIS

(Recurrent Sore Throat)

It is characterized by recurrent or persistent sore throat, swallowing and breathing difficulties, sense of dryness and irritation in throat, offensive breathing, and rarely, dyspnea, chronic hypoxemia and pulmonary hypertension.

Each attack should be treated as for acute tonsillitis. In selected cases of streptococcal disease, penicillin prophylaxis with benzathine penicillin may be given for 3–6 months. The problems usually regress in the subsequent years without any specific treatment. Tonsillectomy is, therefore, usually not necessary. The only definite indications for tonsillectomy are:

- Peritonsillar abscess (quinsy)
- Retrotonsillar abscess
- Seven or more episodes per year

Occurrence of one or more of the following complications following tonsillectomy in some 10% of the children is also a good reason against unnecessary and avoidable surgery.

- Minor hemorrhage
- Postoperative throat infection
- Anesthetic complications
- Pulmonary edema.

ADENOIDS

(Adenoidal Hypertrophy; Hypertrophy of Pharyngeal Tonsils)

Like tonsils, the adenoids are part of the lymph tissues that circle the pharynx (Waldeyer ring) and are susceptible to infection and hypertrophy to such a magnitude that almost the whole vault of nasopharynx may be filled.

Clinical Features

Adenoidal hypertrophy may interfere with the passage of air through the nose, resulting in mouth-breathing



Fig. 26.3: Adenoid facies. Note the consistently open mouth.

(more so when the child lies supine during sleep). With development of gross adenoidal hypertrophy, the child tends to keep the mouth open during day time as well.

Accompanying manifestations include dryness of mouth and lips, persistent rhinitis, pharyngitis, snoring, nasal voice, offensive breath, impaired taste, bad smell, harassing cough, impaired hearing and chronic otitis media. Eventually, the child develops dull expression with open mouth and maloccluded teeth, the so-called **adenoid facies** (Fig. 26.3). School performance suffers. In a few cases, respiratory insufficiency may cause apneic spells, leading to arterial hypertension and, eventually, cor pulmonale.

Diagnosis

Clinical impression of adenoid needs to be confirmed by digital palpation during the first few years of life. Later, indirect visualization with a pharyngeal mirror or fiber optic bronchoscope, or a lateral pharyngeal X-ray may help in confirming the diagnosis.

Treatment

Adenoidectomy leads to significant relief and in improvement of child's condition.

CROUP SYNDROME

Croup is defined as an LRTI characterized by brassy cough, often (not always) accompanied by stridor, hoarseness and respiratory distress.

EPIGLOTTITIS

It is an emergency characterized by URTI, fever, dysphagia, noisy breathing, brassy cough, and respiratory distress with chest retractions (including suprasternal).

Etiologic pathogen is usually Hib though some cases may be caused by *Staphylococcus aureus*, group A streptococci and *Streptococcus pneumoniae*. Treatment

comprises of antibiotics to cover Hib (cefotaxime, ceftriaxone), humidified oxygen and adequate hydration. Intubation and tracheostomy and even short-term ventilation may be needed in some cases. Prognosis with timely treatment is good.

LARYNGOTRACHEOBRONCHITIS

(Infectious Croup)

It is characterized by URTI followed by brassy cough, stridor, respiratory distress with chest retractions (sternal and suprasternal), restlessness from hypoxemia and cyanosis. Etiologic pathogens are invariably viruses (parainfluenza type 1, RSV, parainfluenza types 2 and 3, influenza virus, adenoviruses, rhinoviruses).

Treatment comprises of humidified oxygen, adequate hydration and nebulization with epinephrine and/or intramuscular (IM) injection dexamethasone. Readiness for intubation, tracheostomy and even ventilator support in severe cases is advisable.

Spasmodic Croup

It is characterized by sudden onset of brassy cough and stridor, sometimes preceded (not always) by an URTI. It subsides without any treatment within a few hours, though recurrence may be there in the subsequent days. Etiology remains unclear. Treatment comprises nursing of the child in a well-humidified room.

FOREIGN BODY IN LOWER RESPIRATORY TRACT

Toddlers often aspirate foreign bodies, such as peanuts, almonds, groundnut seeds, grains and pulses. Occasionally, small metallic coins may also be inhaled, though, more often, these are swallowed.

Clinical Features

- There is a sudden paroxysm of cough with congestion of the face and almost a state of suffocation.
- If the foreign body fails to be coughed out, it may cause partial or complete obstruction of the main bronchus.
- Partial obstruction results in massive emphysema.
- Complete obstruction of main bronchus leads to a massive collapse (atelectasis).
- A few days later, the child may be brought to the hospital with signs and symptoms of pneumonia.
- Further delay may result in development of the lung abscess, or bronchiectasis.

Diagnosis

- History of a sudden paroxysm of violent cough, clinical findings of pneumonia, collapse, emphysema, etc.
- Bronchoscopy.
- Radiology, provided it is a metallic foreign body (Fig. 26.4).

Management

It is aimed at removing the foreign body (in most cases by bronchoscopy) and administration of appropriate antibiotics in case of infection.

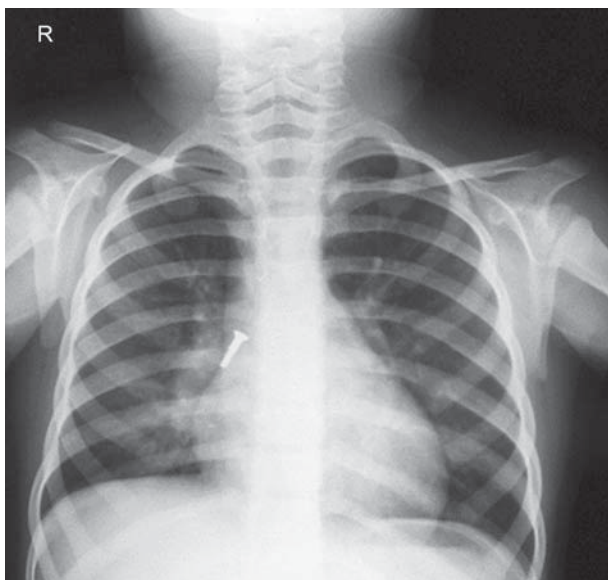


Fig. 26.4: Chest X-ray showing inhaled foreign body (a bolt) in the right bronchus.

ACUTE BRONCHITIS

It is a febrile illness, bacterial or viral in origin, characterized by dry cough (which is worst at night), wheezing and mild constitutional symptoms. Cough becomes productive after about 5 days.

Important chest findings are the widespread rhonchi and coarse crepitations. Some tachypnea is often present. X-ray chest shows nothing significant except for the increased bronchial markings in some of the cases only. Treatment consists in giving a suitable antibiotic, a cough expectorant, and an antipyretic. Warm, moist air is of advantage. With this treatment, most of the patients recover in 7–10 day's time but cough may continue for a month or so. Chronic bronchitis is seen less frequently in pediatric practice.

BRONCHIOLITIS

It is a serious illness, characterized by inflammation of bronchioles, causing severe dyspnea. Infants are the most likely candidates.

Etiopathogenesis

The exact etiology is not clear. An overwhelming majority has a viral etiology. RSV* leads the list followed by influenza viruses, adenovirus, herpes virus, parainfluenza virus; rarely, primary atypical pneumonia organisms (*Mycoplasma pneumonia species*) may be responsible for bronchiolitis.

Certain bacteria (*Hemophilus influenzae*, *Pneumococcus*, *Streptococcus hemolyticus*) and allergy have also been incriminated. However, there is no convincing evidence in support of this. As a result of inflammation, exudate,

edema and contraction of the circular musculature of the bronchioles, there occurs a sort of partial obstruction in the lumen of the bronchioles followed by trapping of the air within the alveoli, resulting in areas of emphysema during expiration. The trapped air gets absorbed when obstruction becomes complete, causing areas of collapse (atelectasis). Finally, hypoxemia (from poor ventilation and diffusion) and respiratory acidosis (from CO₂ retention) may occur.

Epidemiology

Bronchiolitis is more or less confined to winter and early spring and occurs globally. It is primarily a disease of the first 2 years of life, the peak incidence occurring around 6 months of age. Even neonates (especially preterm) may suffer from bronchiolitis. Both epidemic and sporadic forms occur.

Clinical Features

Most cases of bronchiolitis have a mild illness and may not even report to a medical facility. Manifestations are mild and settle within a few days without any medical intervention.

- Following a mild upper respiratory tract infection, bronchiolitis abruptly manifests with dyspnea (rapid shallow breathing) and prostration.
- Cough is either absent or simply mild.
- Mild to moderate fever is usually present.
- If dyspnea is marked, air hunger, flaring of alae nasi, chest retractions and cyanosis may be there.
- Dehydration and respiratory acidosis may complicate the clinical features.
- Chest signs include intercostal, subcostal and suprasternal retractions, hyper-resonant percussion note (this is because of emphysema which may also push the liver and spleen down), diminished breath sounds and widespread crepitations, and wheezing.

Differential Diagnosis

Bronchiolitis requires to be differentiated from:

- Asthma (known for frequent exacerbations).
- Bacterial pneumonia (wheezing either absent or only mild).
- Foreign body in trachea (history of foreign body {FB}, localized wheeze, signs of collapse/emphysema).

CONGESTIVE CARDIAC FAILURE

(Cardiomegaly, Tender Hepatomegaly, Fine Crepitations, Pedal Edema)**

Diagnosis

Diagnosis is generally obvious from the clinical presentation and good chest examination.

* Notwithstanding earlier impression, according to the observations of World Health Organization (WHO), RSV infection is a common and an important cause of acute lower respiratory infection (ALRI) in infants and children even in the developing countries, resulting in acute bronchiolitis, pneumonia and acute exacerbation of asthma.

** Bronchiolitis may per se cause CCF as one of its complications.



Fig. 26.5: Bronchiolitis. Note the remarkable hyperinflation of both lungs in the chest X-ray (CXR).

- Chest X-ray shows hyperinflation (emphysema), prominent bronchovascular markings and small areas of collapse (Fig. 26.5).
- Fluoroscopy (screening) reveals low-lying diaphragm with limited movements. Lungs are characteristically overinflated and intercostal spaces are wide.
- Rapid diagnostic test for identifying RSV is available. It employs monoclonal antibodies. In clinical practice, it is usually not needed.

Complications

These are listed in Box 26.6.

Treatment

Mild bronchiolitis can be easily managed at home in a humidified environment, provided that respiratory distress is not significant. Severe bronchiolitis is an emergency. The management, though mostly symptomatic, warrants hospitalization. General measures include:

- Humidified oxygen inhalation through face mask or head box. Pulse oximetry monitoring should ensure that oxygen saturation remains >92%
- Atmosphere well-saturated with water vapors
- Hypertonic saline (3%) nebulization

Box 26.6 Complications of acute bronchiolitis

Short-term

- Rapidly progressive exhaustion, anoxia and death.
- Dehydration and electrolyte imbalance with respiratory acidosis.
- Congestive cardiac failure.
- Bacterial invasion—bronchopneumonia, acute otitis media.

Long-term

- Bronchiolitis obliterans in which bronchioles are obliterated by nodular masses consisting of granulation and fibrotic tissue. Chest X-ray suggests miliary mottling-like picture.
- Hyperlucent lung syndrome, also called Swyer-James syndrome.

- Epinephrine nebulization
- Mild sedation
- Postural drainage
- Intravenous fluids to combat dehydration
- Infant's positioning—preferably sitting at 30–45 angle; head and neck slightly flexed.
- **Antibiotics:** Since exact etiologic diagnosis is practically impossible in clinical practice, an antibiotic cover may be given on the presumption of a causative or superimposed bacterial infection. Else, it has no role.
- **Bronchodilators: Yes or No?:** These are better avoided since, rather than doing any good, they may increase the cardiac output and restlessness. If indeed indicated in case of poor response to general measures, recommended therapy should be in the form of salbutamol or epinephrine (racemic or levo), preferably by nebulization.
- **Steroids** are no longer recommended.
- Continuous positive airway pressure (CPAP), mechanical ventilation or extracorporeal membrane oxygenation (ECMO) may be indicated in cases developing respiratory failure.
- **Antiviral drugs:** Generally, antiviral therapy is not needed. Severe bronchiolitis resulting from respiratory syncytial virus in an infant with a risk factor (immunodeficiency, congenital heart disease, cystic fibrosis or other chronic lung disease, extreme prematurity/very low birthweight {VLBW}) is best treated with the antiviral agent, ribavirin (Virazid). It is available as sterilized lyophilized powder to be reconstituted for aerosol therapy. Treatment is carried out using a small particle aerosol generator (SPAG) for 12–18 hours a day for at least 3 days but not more than 7 days. A consistent monitoring of both patient and equipment is vital, especially if the subject is in need of assisted ventilation. Therapy with ribavirin is expensive, one 6 g vial costing £ 200 (approximately ₹ 20,000). Moreover, it is teratogenic.

Prophylaxis

For immunoprophylaxis, See Chapter 10 (Immunization).

Prognosis

Overall prognosis is good. In a few cases (1%), deaths may occur in spite of best of treatment.

PNEUMONIAS

The term *pneumonia* refers to infection of the lung parenchyma which may be primary or secondary to acute bronchitis and/or bronchiolitis complicating an upper respiratory tract infection.

Classifications

- **Etiologic classification**
 - **Bacterial:** *Streptococcus pneumoniae* (Pneumococcus), *Staphylococcus*, *Hemophilus influenzae*, *Escherichia coli*, *Klebsiella*, *Hemophilus pertussis*, *Mycobacterium tuberculosis*

- **Viral:** Respiratory syncytial virus, influenza, parainfluenza, adenoviruses; measles, chickenpox
- **Atypical organisms:** *Chlamydia*, *Mycoplasma pneumonia species*
- **Fungal:** *Pneumocystis carinii* (*jroveci*), thrush, coccidioidomycosis, histoplasmosis, blastomycosis (usually in immunocompromised subjects)
- **Protozoal:** *Toxoplasma gondii*, *Entamoeba histolytica*
- **Rickettsial:** Typhus, Rocky mountain spotted fever
- **Miscellaneous:** Aspiration pneumonia (vomitus, amniotic fluid in newborn, drowning, foreign body, chemicals like kerosene oil and liquid paraffin, in-stilled oil in nose); Loeffler pneumonia; hypostatic pneumonia; ventilator-associated pneumonia.

■ **Anatomic classification**

- **Bronchopneumonia:** Patchy involvement of lungs
- **Lobar pneumonia:** One or more lobes of a lung involved
- **Interstitial pneumonia/pneumonitis:** Alveoli or interstitial tissue between them affected. It is more or less a radiologic diagnosis.

■ **Classification based on acquisition**

- Congenital pneumonia
- Community-acquired pneumonia
- Hospital-acquired pneumonia.

■ **Classification based on chronicity**

- Acute pneumonia
- Recurrent pneumonia
- Chronic (persistent) pneumonia.

■ **WHO classification**

- Very severe pneumonia
- Severe pneumonia
- Pneumonia (not severe)
- No pneumonia.

Important Definitions

These are listed in Box 26.7. Box 26.9 lists some rules of thumb in bacterial pneumonia.

Clinical Features

The onset is usually sudden with high fever, chills, cough and respiratory distress. Active movements of the alae

Box 26.8

Predisposing factors for recurrent and chronic (persistent) pneumonia

Immunodeficiency

- PEM
- HIV

Congenital respiratory malformations

- Tracheoesophageal fistula
- GER

Congenital heart disease

- Ventricular septal defect

Defective clearance of airway secretions

- Cystic fibrosis

Chronic pulmonary diseases

- Tuberculosis
- Bronchiectasis
- Asthma.

Abbreviations: PEM, protein energy malnutrition; HIV, human immunodeficiency virus; GER, gastroesophageal reflux.

Box 26.9

Certain rules of thumb in bacterial pneumonias

- Pneumococcal pneumonia accounts for 80–90% of bacterial pneumonias in childhood. After 3 years of life, it is responsible for a vast majority of bacterial pneumonias
- **In neonates and up to 2 months of age:** Gram-negative organisms (*E. coli*, *Klebsiella*, *Pseudomonas*, *Proteus*); *Staphylococcus*
- **From 2 or 3 months to 3 years:** *Hemophilus influenzae*, *Streptococcus pneumoniae*; *Staphylococcus* in special situations
- **More than 3 years:** Invariably *Pneumococcus*
- Staphylococcal pneumonia occurs in neonatal period, but may occur at any age in special situations.

nasi, grunting, expiration and lower costal recession with some cyanosis are alarming manifestations. In some cases, diarrhea, vomiting convulsions and chest pain (referred to abdomen) may be present.

Chest signs of consolidation include diminished movements of affected side, increased vocal fremitus and resonance, dullness, diminished breath sounds, and bronchial breathing. Crepitations denote beginning of resolution. There is no shifting of mediastinum. Chest signs of bronchopneumonia include tachypnea, normal or harsh breath sounds and diffuse harsh crepitations spread all over in both the lungs.

World Health Organization has recommended that very fast breathing, especially in association with cough, difficult breathing or indrawing of chest, must always be considered a reflection of pneumonia, unless proved otherwise. Fever undoubtedly causes elevation in respiratory rate. But, the effect is only weak, say 2–3 breaths per 1°C rise above 37°C per minute. The cut-off point for high respiratory rate is over 60 per minute upto 2 months of age, over 50 per minute between 2 months and 12 months and 40 per minute between 12 months and 5 years.

In debilitated infants and children, despite the presence of extensive pneumonia, signs and symptoms may not be as classical as described above. The diagnosis of pneumonia in such cases is often made following detailed examination and a chest radiograph. Presence of certain predisposing factors (Box 26.10) should arouse suspicion for *Staphylococcal pneumonia*.

Box 26.7

Certain definitions

- **Congenital pneumonia:** A pneumonia in which the neonate presents right at birth as a result of hematogenous or ascending infection or aspiration.
- **Persistent pneumonia:** Chronic nonresolving pneumonia in which radiological findings persist for over 1 month. Predisposing factors are given in Box 26.8.
- **Recurrent pneumonia:** Two or more episodes in 1 month, provided that the earlier episode showed complete resolution with adequate therapy or three or more episodes any time in life.
- **Community-acquired pneumonia:** A pneumonia caused by pathogens outside the hospital settings, i.e. in the community per se.
- **Hospital-acquired pneumonia:** A pneumonia that develops during hospital stay, at least after 48 hours of admission and not incubating at the time of admission to the facility. It includes ventilator-associated pneumonia (VAP), postoperative pneumonia and healthcare-associated pneumonia.

Box 26.10**Predisposing factors for staphylococcal pneumonia**

- Infectious diseases of childhood, such as measles and chickenpox.
- Staphylococcal infections elsewhere in the body, e.g. skin (furunculosis), throat, etc.
- Debilitating illnesses, e.g. advanced protein energy malnutrition (PEM), cystic fibrosis, malignancies, etc.
- Hypogammaglobulinemia.
- Immunosuppressive therapy.



Fig. 26.6: Subcutaneous emphysema in an infant with bronchopneumonia.

Complications

The complications include:

- Pleural effusion or emphysema
- Collapse
- Pneumatocele
- Lung abscess
- Bronchiectasis
- Subcutaneous emphysema (Fig. 26.6)
- Metastatic spread: Meningitis, septic arthritis, osteomyelitis, etc. Of the various types, staphylococcal pneumonia carries the worst prognosis.

Diagnosis

Besides clinical suspicion, a chest X-ray (PA view, ordinarily) is most reliable to detect the type and extent of lesions. CXR findings suggesting bronchopneumonia include multitude of diffuse patchy consolidations, usually involving both the lungs.

CXR findings suggesting lobar pneumonia (consolidation) include a homogenous opacity occupying the anatomic area of a lobe without any mediastinal shift, usually involving only one lung (Fig. 26.7). Detection of pleural effusion, pyopneumothorax or pneumatoceles (small inflated abscesses) highly favor the diagnosis of *Staphylococcal pneumonia* (Figs 26.8 and 26.9).

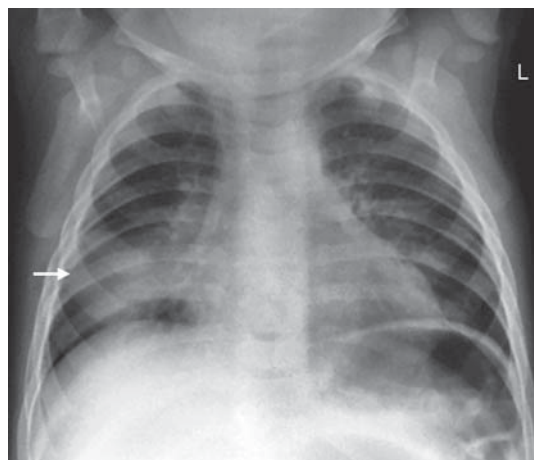


Fig. 26.7: Lobar pneumonia. Note the patch of consolidation in right lower lobe with blurring of the right heart border (Silhouette sign).



Fig. 26.8: *Staphylococcal pneumonia*. Demonstration of pneumatoceles is regarded pathognomonic of staphylococcal pneumonia. It usually occurs during infancy secondary to staphylococcal infection elsewhere in the body. Unless treated energetically, serious complications are a rule.

Nonradiopaque foreign bodies may produce multiple abscesses or pneumatoceles, resulting in a radiologic picture simulating that seen in *Staphylococcal pneumonia*. Miliary mottling constitutes another important differential diagnosis. Recently, **lung ultrasonography** has been recommended as a more accurate modality for detecting pneumonia in a situation where CXR fails to show highly suspected pneumonia. Recurrent pneumonia and chronic (persistent) pneumonia must arouse suspicion of certain pre-existing conditions (Box 26.11).

Treatment

Once the diagnosis of pneumonia is arrived at, it should be decided whether the child needs just outpatient treatment or hospitalization (Box 26.12). Most children suffering from viral pneumonia have mild illness. They may be treated as outpatients.

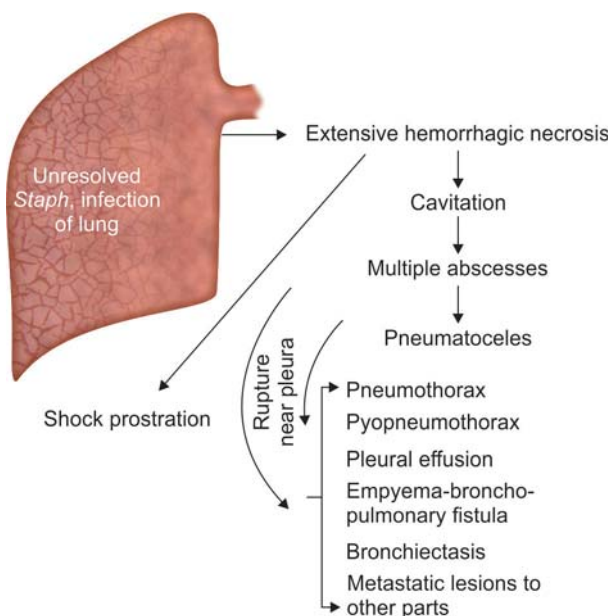


Fig. 26.9: *Staphylococcal pneumonias*. Natural history of development of complications in *Staphylococcal pneumonia*.

Box 26.11

Certain pre-existing conditions in recurrent or chronic (persistent) pneumonia

- Abnormalities of antibody production such as agammaglobulinemia
- Cystic fibrosis (CF)
- Cleft palate
- Congenital bronchiectasis
- Immotile cilia syndrome
- Tracheoesophageal fistula
- Gastroesophageal reflux disease (GERD)
- Increased pulmonary blood flow
- Deficient gag reflex
- Foreign body
- Tuberculosis
- Abnormalities of polymorphonuclear leucocytes
- Neutropenia.

Box 26.12

Indications for hospitalization in pneumonia

- Child is sick enough, manifesting features of hypoxia (respiratory distress, cyanosis, restlessness, seizures)
- **High-risk factors:**
 - Immunodeficiency
 - Cystic fibrosis
 - Congenital heart disease, etc.
- Poor response to treatment provided as an outpatient.

Antibiotics in Community-acquired Pneumonia

A specific antibiotic agent is dictated by the anticipated causative agent rather than the anatomic type of pneumonia.

Pneumococcal Pneumonia

Penicillin is the drug of choice for pneumococcal pneumonia (*Streptococcus pneumoniae* pneumonia) which is the usual pneumonia encountered in children beyond 1 year of age. In uncomplicated cases, it leads to dramatic response, causing complete resolution in 7–14 days. In case of penicillin hypersensitivity, amoxicillin or a cephalosporin

like cefazolin makes an appropriate alternative agent in 437 sensitive strain.

Emergence of multidrug resistance strains (MDRS) of *Streptococcus pneumoniae* (that causes not only pneumonia but also acute otitis media {AOM}, acute sinusitis, acute bronchitis, etc.) fail to respond to penicillin and other β -lactams and non- β -lactams, including cephalosporins. In such a situation, it is advisable to consider use of a β -lactamase inhibitor along with a β -lactam, say amoxicillin-clavulanate (co-amoxiclav) or ampicillin-sulbactam for a gratifying outcome.

Saphylococcal Pneumonia

A penicillinase-resistant penicillin (cloxacillin) plus ampicillin is the best choice. Alternatively, vancomycin or clindamycin may be employed.

Hemophilus Influenzae

Ampicillin and amoxicillin/co-amoxiclav are good enough for mild disease. For severe illness, choices are:

- Ampicillin plus chloramphenicol or ceftriaxone
- Cefotaxime or ceftriaxone.

Gram-negative Organisms

- ***Klebsiella*:** A combination of cefotaxime or ceftriaxone plus an aminoglycoside (amikacin, netilmicin, gentamicin, etc.) is the therapy of choice.
- ***Pseudomonas pneumonia*:** Treatment of choice is ceftazidime, piperacillin or ticarcillin alone or in combination with gentamicin or amikacin.
- ***Pneumocystis carinii* (jerveci) pneumonia** (interstitial plasma cell pneumonia)
- **Cotrimoxazole** in very high doses (20 mg/kg/day with reference to trimethoprim).
- **Thrush pneumonia (pulmonary candidiasis):** Only amphotericin B or 5-fluorocytosine.
- **Tuberculous pneumonia:** Antituberculous therapy (ATT) which is discussed elsewhere in this very chapter.
- **Viral pneumonia:**
 - **Respiratory syncytial virus:** Ribavirin aerosolization
 - **Influenza virus:** Oseltamivir, peramivir
 - **Loeffler pneumonia:** Loeffler syndrome
 - **No antibiotic:** Only symptomatic treatment.
 - **Mycoplasma pneumoniae (Primary atypical pneumonia):** Erythromycin or tetracyclines in case of grown-up children (>8 years).
- **Aspiration pneumonia:** Use of prophylactic antibiotics is usually recommended. Needless to say, these recommendations are subject to changes which may be warranted following receipt of culture and sensitivity report.

Antibiotics In Hospital-acquired Pneumonia

Recommended drugs vary with the likely pathogen(s):

- **Gram-negative bacilli:** Generally, aminoglycosides (amikacin, netilmicin, gentamicin).
- ***Klebsiella*:** Third generation cephalosporins.

- 438 ■ *Pseudomonas aeruginosa*:** Piperacillin with tozabactam, ticarcillin with clavulanate, ceftazidime or quinolones.
- ***Staphylococcus aureus*:** Vancomycin or cloxacillin; quinolones and cefazolin are good alternatives.
 - ***Anaerobes*:** Metronidazole and clindamycin.

General Measures

- Good nursing care
- Bed rest
- Suction to remove secretions from tracheobronchial tree
- Oxygen
- Symptomatic treatment for cough, restlessness, fever and pain
- Adequate fluid and dietary intake
- Physiotherapy—breathing exercises during recovery are of value.

Treatment of Complications

- Treatment of congestive cardiac failure, if present.
- Surgical intervention may be needed in subjects who have developed complications like empyema or tension pneumothorax, a fairly common occurrence in staphylococcal pneumonia.

Finally, a word of caution. The widespread practice of employing sodium bicarbonate in cases of tachypnea (unless accompanied by documented metabolic acidosis) must be discouraged. Such an administration may prove counterproductive by causing respiratory alkalosis.

Prognosis

Prognosis is generally good following appropriate and in time treatment.

BRONCHIECTASIS

Definition

Bronchiectasis is defined as a permanent dilation of the bronchi and bronchioles, as a result of obstruction and/or infection. Consequent to this, there is cavitation of the bronchial wall and tissue destruction. Collapse, emphysema and pneumonia usually accompany bronchiectasis.

Etiopathogenesis

As already mentioned, bronchial occlusion and inflammation over a prolonged period form the cornerstone of the natural history of bronchiectasis. If the occlusion is significant, there results collapse distal to and dilation proximal to the site of obstruction. Partial obstruction first causes emphysema in the distal part. With the passage of time and further progression of the lesion, coupled with repeated infections, the classical picture results ultimately.

Depending on the shape of the dilated part, bronchiectasis has been classified as saccular, cylindrical or fusiform. In a large majority of the children, it is unilateral, generally involving the posterior basal segment of the left lower lobe.

The common conditions with which bronchiectasis may be associated or which it may follow are:

- Obstruction due to foreign body.
- Obstruction due to collection of thick mucus as in cystic fibrosis, bronchial asthma or chronic bronchitis.
- Infections, e.g. measles, pertussis, pneumonia (staphylococcal, in particular), sinusitis or tuberculosis.

In addition to acquired bronchiectasis, the disease may occur secondary to congenital collapse. The so-called **Kartagener syndrome** is characterized by dextrocardia (usually with situs inversus), chronic bronchitis with bronchiectasis at a later stage and sinusitis. Bronchiectasis occurs rather late, usually in early 20s. Chronic bronchitis is what is usually encountered in childhood. Chronic otitis media like chronic sinusitis is common. Survivors have high incidence of sterility. The origin of the syndrome is ascribed to generalized defect of ciliary motility right from the embryonal stage. Hence, the nomenclature immotile cilia syndrome or dyskinetic cilia syndrome. The most common organism found in the sputum of children with this disease is *Staphylococcus*.

Clinical Features

- The onset is usually insidious with persistent or recurrent cough, productive of copious mucopurulent sputum. The latter is foul-smelling and has postural relationship. Likewise, patient's breathing also carries bad smell. Some fever and recurrent attacks of respiratory infections are frequent.
- In advanced cases, dyspnea, cyanosis, clubbing and hemoptysis may also be present.
- The characteristic auscultatory finding is the localized crepitations, repeatedly found over the affected area. Other signs suggestive of collapse-consolidation may also be present.

Diagnosis

- Clinical suspicion.
- Radiology—X-ray chest shows increased bronchovascular markings, extending towards the base of the lung. Later, areas of cavitation may become apparent.
- Bronchography (it should be preceded by bronchoscopy) is essential to localize and establish the extent of bronchiectasis.
- Bacteriologic examination of sputum or secretions.

Treatment

- **Appropriate antibiotic cover:** Systemic antibiotics are to be preferred.
- **Postural drainage:** The use of bronchodilator aerosol is of added advantage in this behalf.
- Breathing exercises.
- Surgical intervention to remove the affected lobe(s), provided that medical treatment, given over a 12-months period, has failed.

Prognosis

With the aforesaid regimen, prognosis is generally good.

DRY PLEURISY

(Plastic Pleurisy)

In this condition, small serous fluid and adhesions develop between the pleural surfaces, at times severe enough to inhibit lung movements.

Etiology

The causes include upper and lower respiratory infections, tuberculosis, acute rheumatic fever and other mesenchymal diseases.

Clinical Features

On top of the manifestations of the primary disease, the child has pleural pain which gets exaggerated by deep breathing and may be referred to the shoulder or the back. As a result of pain, grunting and guarding of respiration may develop, compelling the child to lie on the affected side.

Physical examination shows some dullness on percussion and diminution of breath sounds in case of thickened pleura or a thick layer of exudates. A rough to and fro friction sound, pleural rub may be heard early in the disease. Often, pleurisy may be asymptomatic.

Diagnosis

Chest X-ray shows a diffuse haziness at the pleural surface or a dense well-defined shadow. Differential diagnosis includes pleurodynia, rib fracture, herpes zoster, etc.

Treatment

This is primarily of the underlying disease.

PLEURAL EFFUSION

It is the collection of serous fluid (in empyema, it is the thick purulent fluid, i.e. pus) in the pleural cavity (between parietal and visceral pleura).

Pleural effusion is relatively less frequent in children; almost all cases are seen beyond 5 years of age. Pleural fluid may be transudate (clear with protein <3 g% and no cells) or exudate (straw-colored with protein >3 g% and lymphocytes) (Table 26.3).

Etiology

Tuberculosis is responsible for majority of the cases followed by pneumonia, CCF, constrictive pericarditis and hypoproteinemic states (nephrotic syndrome, kwashiorkor, protein-losing enteropathy, hepatic failure). In a small proportion, thoracic lymphoreticular malignancy may be the cause.

Pleural effusion results from discharge of the caseous material of a peripheral (subpleural) primary focus or enlarged regional lymph node. Hematogenous, or local spread as also allergic reaction to tuberculous proteins too can cause pleural effusion.

Table 26.3: Differences between pleural transudate and exudate

Parameters	Transudates*	Exudates	
		Tuberculous	Pyogenic
Appearance	Clear	Straw-colored	Turbid
Protein	<3 g/dL	>3g/dL	>3 g/dL
Pleural fluid protein/serum-protein ratio	<0.5:1	>0.5:1	>0.5:1
Pleural fluid lactate dehydrogenase (LDH)/Serum LDH ratio	<0.6:1	>0.6:1	>0.6:1
pH	>7.2	<7.2	<7.2
Glucose	>40 mg/dL	<40 mg/dL	<40 mg/dL
Cellularity	Absent	Lymphocytes	Polymorphs

*May accompany nephrotic syndrome, CCF, cirrhosis, anemia with hypoproteinemia, kwashiorkor.

Clinical Features

- Onset is usually subacute with manifestations, such as high fever, cough, chest pain on affected side (that worsens on deep breathing and coughing), reflex abdominal pain in case of basal effusion and weight loss.
- Breathlessness may occur depending on rapidity of accumulation and magnitude of effusion.
- Physical examination reveals decreased chest movements on affected side, mediastinal shift to the opposite side, fullness of the intercostal spaces, decreased vocal fremitus, stony dull percussion note, pleural rub, decreased vocal resonance and decreased breath sounds. Above the effusion level, egophony (marked hyper-resonance due to compensatory emphysema) may be elicited. Percussion note in axilla may be at a higher level. This is what is termed as **Ellis curve**.

Diagnosis

X-ray chest shows a uniform opacity with a curved fluid line which may become horizontal when air is also coexisting (Fig. 26.10). There is a definite mediastinal shift to the opposite side. Ultrasonography assists in localizing the fluid better.

Pleural tap See Chapter 49 (Pediatric Practical Procedures) and examination of the fluid confirms the diagnosis. Straw-colored fluid with high-protein content and lymphocytic response (exudate) strongly favors tuberculous pathology.

Treatment

Specific chemotherapy depends on the etiology of pleural effusion, most cases needing antituberculous therapy. Therapeutic thoracentesis (also called **thoracocentesis**) is indicated in case of large pleural effusion causing respiratory distress. As a rule, quantity of aspiration should not exceed 20–30 mL.



Fig. 26.10: Pleural effusion. Note the horizontal fluid line due to presence of air on top of effusion. Pure pleural effusion causes uniform opacity with curved upper border.

EMPYEMA THORACIS

Definition

By definition, the term, **empyema**, denotes collection of thick pus in the pleural cavity. It is fairly common in infancy.

Etiology

The most common organism responsible for empyema is *Staphylococcus*. Infrequently, *Streptococcus pneumoniae*, *Hemophilus influenzae*, and even *Mycoplasma pneumonia* account for a small proportion of the cases. Usually it is the outcome of a complication of:

- Pneumonia (usually staphylococcal)
- Lung abscess
- Bronchiectasis
- Subdiaphragmatic abscess/liver abscess (rupture)
- Septicemia
- Metastatic spread of suppurative foci from distant lesions such as osteomyelitis.

Clinical Features

- Clinical manifestations, if present, are those of pneumonia.
- Fever, dyspnea, cough, chest pain (which may be referred to the abdomen), and toxemia are the usual presenting features.
- In case of marked respiratory distress, the child is cyanotic too.
- Long-standing cases develop clubbing, anemia and other manifestations of malnutrition.
- A category of children, in spite of empyema, do not manifest the symptomatology described above. They may, however, suffer from growth failure and vague symptoms. Empyema in such cases is usually detected when the child is subjected to a detailed clinical check-up.

- Chest signs are similar to pleural effusion and include diminished movement on the affected side, widening and dullness (at times, edema) of the intercostal spaces, dull percussion note, reduced vocal fremitus and vocal resonance, diminished air entry* and mediastinal shift to the opposite side.

It is worth remembering that empyema must be ruled out in any infant with localized dullness of the percussion note. The term **empyema necessitance** implies a pulsatile swelling over the chest.

Complications

- Bronchopleural fistulas
- Pyopneumothorax
- Purulent pericarditis
- Pulmonary abscesses
- Peritonitis
- Osteomyelitis of ribs
- Meningitis
- Arthritis
- Septicemia.

Diagnosis

- Clinical suspicion
- **X-ray chest:** In addition to the mediastinal shift to the opposite side, it shows a diffuse density suggestive of pleural fluid. In most of the cases, the opacities are basal and costophrenic angle is obliterated. Loculated empyema may, however, occur in the fissures or at the apex.
- **Diagnostic pleural tap:** The fluid is purulent (turbid) and should be examined biochemically (for high protein and low sugar) as also bacteriologically (for causative pathogens).

Treatment

- Antibiotics should be started as soon as the diagnosis is arrived at. Staphylococcal empyema is best treated with systemic penicillin G or, in case of penicillinase-producing organisms, with cloxacillin or vancomycin. Pneumococcal empyema shows a gratifying response to penicillin G. For *H. influenzae* empyema, ampicillin, chloramphenicol or third-generation cephalosporin is recommended.

Response to staphylococcal empyema is slow. Antibiotic therapy should, therefore, be continued for 3–4 weeks. Closed continuous intercostal drainage is strongly recommended. It needs to be controlled by underwater seal or continuous suction. Controlling empyema by this method should be the choice rather than the multiple aspirations of the pleural cavity.

- Surgical drainage after rib resection (thoracotomy or thoracotomy) may be resorted to in case of severe respiratory difficulty, when improvement fails to occur after 3 weeks, in loculated pus, or in the presence of marked mediastinal shift.

* Unlike in adults, an infant's breath sounds may be heard in spite of considerable empyema thoracis.

In addition to the aforesaid, symptomatic measures, as and when needed, should be resorted to.

Prognosis

Empyema is a serious disease. Before antibiotic era, the prognosis used to be very bad. Today, following proper treatment, in-time, prognosis is excellent in the long-run. Some cases may be left with restrictive disease.

LUNG ABSCESS

In India and other developing countries, lung abscess is relatively common.

Etiology

- **Single abscess:** Usually due to pneumonia, tuberculosis or foreign body and, occasionally, following rupture of amebic liver abscess into lung or superadded infection of hydatid cyst.
 - **Multiple abscesses:** Usually due to pneumonia, tuberculosis, cystic fibrosis, fungal infection, leukemias, agammaglobulinemia, etc.
- If an abscess fails to resolve, it may cause pleurisy, pleural effusion or empyema.

Clinical Features

- **Acute abscesses** usually develop during the course of staphylococcal pneumonia and resolve spontaneously with suitable treatment.
- **Chronic abscesses** have insidious onset with fever, persistent cough and foul-smelling sputum. At times, dyspnea and chest pain may be there. Clubbing develops if the patient remains without treatment over a prolonged period.
- Chest signs are usually those of consolidation with bronchial breathing.

Diagnosis

X-ray chest shows characteristic opacities. The cavities may show fluid levels.

Treatment

- Appropriate antibiotics
- Postural drainage
- Breathing exercise
- Surgical resection of the particular segment or lobe should only be done when the medical measures have failed. Surgical drainage is obsolete now.

BRONCHIAL ASTHMA

(Hyper-Reactive Airway Disease)

Definition

Bronchial asthma, a chronic inflammatory disorder of the lower airway, is characterized by paroxysms (bouts) of

dyspnea, wheezing (predominantly expiratory) and cough, as a result of temporary narrowing of the bronchi by trio of bronchospasm, mucosal edema and thick secretions. **441**

Most cases have had its origin in the first 2 years of life. The peak incidence is, however, seen in 5–10 years of age group. Boys suffer twice as much as the girls. The illness too is more severe in them. Incidence in school-going age is around 2%.

Etiopathogenesis

Triggers/Excitatory Factors

- **Allergy to certain foreign substances:**
 - Inhalants like pollen, smoke, dust* and powder;
 - Foods like egg, meat, wheat and chocolate;
 - Food additives;
 - Drugs like aspirin and morphine. In majority of the asthmatics, it is, however, difficult to find the causative allergen.
- **Respiratory infection:** Usually a viral infection causes mucosal edema and mucous secretion that result in narrowing of the airway.
- **Emotional disturbances:** A row with the siblings or the parents and fear of punishment may operate through vagus and cause bronchospasm.
- **Exercise:** Role of exercise/exhaustion is well-known in the so-called **exercise-induced asthma**. Loss of heat and water from the lower airways leads to a state of mucosal hyperosmolarity. The latter causes release of mediator from the mast cells which result in bronchospasm.
- **Change of climate/weather:** This acts through two mechanisms, namely sudden release of airborne allergens and loss of water and heat from lower airways.
- **Puberty changes:** Endocrinal changes at puberty are known to enhance symptoms of asthma in adolescents.

Predisposing Factors

- **Heredity:** A family history of asthma or some other allergic disorder is often forthcoming
- **Childhood infections:** Measles and pertussis.
- **Constitution:** An asthmatic child is basically labile, highly stung and overconscientious.

Pathophysiology

Factors ending up with lower airway obstruction in asthma include:

- Mucosal inflammation (especially edema)
- Excessive mucosal secretions (mucus, inflammatory cells, cellular debris)
- Bronchial hyper-responsiveness with bronchospasm.

Three types of asthma are:

1. **Extrinsic:** This is IgE-mediated and precipitated by an allergen
2. **Intrinsic:** This is non-IgE-mediated and precipitated by a respiratory infection (usually, viral)

* The house-dust mite, *Dermatophagoides pteronyssinus*, has now been implicated as probably the most important cause of the allergenicity of the house-dust allergens in the environment and loss of heat and water from the lower airways.

442 3. Mixed: This is usually exercise-induced or aspirin-induced following exposure to an allergen which interacts with specific mast cell-bound IgE. Reaction occurs in two phases:

1. **Early phase/reaction:** Within minutes, mast cell releases histamine, leukotriene C, D and E, prostaglandins, platelet-activating factor (PAF) and bradykinin, causing mucosal edema, secretion and bronchospasm. The net result is lower airway obstruction. Premedication with β_2 agonists can inhibit this phase.
2. **Late phase/reaction:** This is characterized by clinical manifestations of asthma. It follows 3–4 hours later with release of mast cell mediators. Unlike the early phase, β_2 agonists cannot inhibit it. However, steroids are capable of inhibiting it. Over and above inflammation two additional factors may contribute to the development of hyper-reactivity of the lower airway, namely:

- Intrinsic defect in the airway
- Abnormal neural control of the airway.

Pathology

Inflammation of the lower airways is considered to be the **cornerstone** of the basic pathology of asthma. The inflammatory changes are characterized by infiltration of the mucosa and epithelium with activated mast cells, T cells and eosinophilia. The mediators of inflammation (leukotriene) released by the mast cells damage the wall of the airway, causing epithelial shedding and mucus secretion.

The so-called **bronchial hyper-reactivity** accompanied by bronchospasm involving smooth muscles is now regarded as secondary to inflammation. Defect in the airway and abnormal neural control of the airway may also contribute to its development. A PAF, supposed to be formed by the inflammatory cells, causes bronchial hyper-reactivity. The net result of inflammation and bronchospasm is characteristic wheeze and respiratory distress. Poorly controlled disease results in collapse and emphysema. Rarely, bronchiectasis may occur.

Clinical Features

The onset of an asthmatic paroxysm is usually sudden, often occurring at night. Occasionally, it is preceded by the so-called **asthmatic aura** in the form of tightness in the chest, restlessness, polyuria or itching. A typical attack consists of marked dyspnea, bouts of cough and chiefly expiratory wheezing. Cyanosis, pallor, sweating, exhaustion and restlessness are often present. Pulse is invariably rapid.

The fulminant attack may subside in an hour or two, sometimes with vomiting or coughing up of viscid secretions. Some expiratory wheezing may, however, continue over several days, though the child is otherwise comfortable. Generally, recurrent asthmatic attacks last over 2–7 or 10 days. Then there is an interval of freedom which may vary from a few days to few months. Children

with severe bronchial asthma over a prolonged period may develop a barrel-shaped chest deformity.

Diagnosis

Though it is usually clear from the clinical profile, the following tests should be carried out for its confirmation:

- **Peak expiratory flow (PEFR) meter:** PEFR is very useful in confirming diagnosis of asthma. The child suspected to be having the disorder is made to stand and breathe in (inhale) deeply. Then, he breathes out (exhales) quickly and hard right into the PEFR meter. The process is repeated thrice and highest of the three readings ascertained for its normal or low level. If the reading is low, the diagnosis of asthma may further be confirmed by bronchodilator reversibility test and steroid test in case bronchodilator therapy fails to cause improvement in the reading.

If PEFR reading is normal and yet asthma is a strong suspicion, diurnal variation test and exercise test may be carried.

- **Chest X-ray (CXR):** An invariable finding is bilateral and symmetrical air trapping with patches of collapse of varying sizes but seldom large, bronchial cuffing and prominent main pulmonary artery.
- **Absolute eosinophil count:** A high eosinophil count lends support to the diagnosis provided that it is not secondary to tropical eosinophilia or steroid therapy.
- **Allergy test:** All attempts should be made to detect the responsible allergen.

Differential Diagnosis

Bronchial asthma should, in particular, be differentiated from cardiac asthma (left heart failure), asthmatic bronchitis, foreign body inhalation, acute bronchiolitis, tropical eosinophilia, whooping cough, and wheeze associated with ascariasis, filariasis and mediastinal lymphadenopathy in tuberculosis or lymphoma. Chronic bronchitis, though uncommon in children, may closely simulate bronchial asthma.

Complications

- Emphysema (most common)
- Collapse (middle lobe on right side)
- Cor pulmonale
- Pneumothorax
- Bronchiectasis
- Tuberculosis in patients on prolonged steroid therapy.

Management of Acute Exacerbation of Asthma

- Specific measures—pharmacotherapy (Table 26.4 and Box 26.13).
- Education directed at child's parents as well as the child.

Specific Measures

Acute mild exacerbation

- β_2 agonists (oral, inhalation metered-dose inhaler {MDI with spacer} or nebulization)

Table 26.4: Drugs employed in asthma

Drugs	Oral dose	Parenteral dose	Aerosol dose
β_2 adrenergic agonists			
Salbutamol (Albuterol)	0.1 mg/kg/dose 3–4 times/day	7.5 μ g/kg in 5–10 min, then 0.1 μ g/min, increase	100–200 μ g (1–2 puffs) every 1–5 hrs every 15 min by 0.1 μ g/kg upto 0.4 μ g/kg/min (IV)
Metaproterenol (Orciprenaline)	0.3–9.5 mg/kg/dose 3–4 times/day		650 μ g (1–2 puffs)
Terbutaline	0.075 mg/kg/dose	0.005 mg/kg dose (IV) 3–4 times/day	250 μ g (1–2 puffs)
Theophyllines			
Aminophylline	4–6 mg/kg/dose	6 mg/kg followed 3–4 times/day	0.9 mg/kg/hr
Theophylline	4–5 mg/kg/dose 3–4 times/day		
Steroids			
Prednisolone	1–2 mg/kg/day		
Hydrocortisone		8–10 mg/kg followed by 1 mg/kg/hr or 3 mg/kg every 6 hr	
Beclomethasone			1–2 puffs 3–4 times/day, maximum 10 puffs/day
Ketotifen Cromoglycate	0.25–0.5 mg BD		1–2 puffs 6 hourly; 1–2 puffs 20 minutes before exercise in EIA

Abbreviations: IV, intravenously; EIA, exercise-induced asthma.

Box 26.13**Long-term pharmacological management of different grades of asthma**

- **Mild intermittent (episodic) asthma:** Oral or inhaled salbutamol or terbutaline as and when required
- **Mild persistent asthma:** Inhaled short-acting β_2 agonists plus inhaled steroids
- **Moderate persistent asthma**
- **Severe persistent asthma:** Inhalation steroids plus long-acting β -agonist and/or slow-release theophylline. Add-on therapy with montelukast yields better control. Poor control is an indication for oral steroids (low-dose alternate-day prednisolone).

- Prednisolone, 1–2 mg/kg/day (O) or inhalation steroids (Table 26.5); if no improvement, follow regimen for moderate exacerbation.

Acute moderate exacerbation

- Oxygen inhalation until oxygen saturation >95%.
- Nebulization with β_2 agonists, every 20 minutes for 1 hour, then 4–6 hourly.
- Prednisolone, 1–2 mg/kg (O) stat and then daily for 5–7 days.

If no improvement, follow treatment for acute severe asthma (vide infra).

Acute Severe Exacerbation

Acute severe asthma, Life-threatening asthma:

- Immediate oxygen inhalation
- Subcutaneous injection of adrenaline
- Nebulization with β_2 agonists (salbutamol or terbutaline) and ipratropium, every 20 minutes
- Intravenous (IV) hydrocortisone, 5 mg/kg/dose, every 6–8 hourly until oral acceptance is in place. If no improvement, either of the following is needed:

Table 26.5: Various types of inhalation devices

- **Metered-dose inhaler (MDI):** This aerosol asthma therapy needs good hand-lung coordination and is, therefore, suitable only for children aged 6 years and beyond (Fig. 26.11). The asthma therapy that is appropriate for administration by MDI include β_2 -adrenergics (salbutamol, terbutaline), atropine derivatives (ipratropium bromide), steroids (beclomethasone, budesonide), and cromoglycate sodium. The dose is administered by taking a puff for 5–7 seconds which can be repeated, if the need be, after a gap of one minute. It cuts short the dose by 10–15 times and the action begins within just 5 minutes. Side effects of the drug are minimized.
- **Space device inhaler (Spacehaler):** This device overcomes the shortcoming of simple MDI and may be in the form of a valved reservoir or inflatable reservoir bag (Fig. 26.12). It has to be attached to the MDI. It can be used even in children under 3 years. The drug delivery is through a mouthpiece. The device safeguards against deposition of drug particles over pharynx by impaction, thereby reducing the incidence of hoarseness and Candida infection accompanying inhalation therapy.
- **Dry powder devices (Rotahaler, Spinhaler, Turbuhaler):** These devices do not need patient's cooperation and are supposed to be useful even in children under 5 years of age (Figs 26.13A and B). However, in actual practice, this does not seem to hold good. Rotahaler is employed for steroid and β_2 -agonist therapy, spinhaler for cromoglycate and turbuhaler for prophylactic steroid therapy.
- **Nebulizers:** Nebulization comprises passage of gas at high velocity, leading to formation of particles of (25 microns at least) a specific size (Fig. 26.14). It is best suited in very sick subjects with acute asthma and in very young infants and children who are not in a position to synchronize. Drugs available for nebulization are β_2 -agonists (salbutamol, terbutaline), steroids and cromoglycate. Nebulization should be for a period of 5–10 minutes at a time. Often, a second nebulization after 2 minutes with a maximum of 6 doses with a maintenance dose at 4–6 hour's interval for 2–3 doses is required.



Fig. 26.11: Metered-dose inhaler (MDI).



Fig. 26.12: Space device inhaler (spacer, spacehaler). It needs to be attached to the MDI and is even suitable for children below 3 years.



Figs 26.13A and B: Dry powder inhaler (Rotahaler). Baby mask attached to the space inhaler which again needs to be attached to the MDI. This device sends the MDI usefull for the infants.



Fig. 26.14: Nebulizer therapy is the most effective means of treating a severe attack of asthma, especially when the patient is an infant or a very sick child not able to synchronize.

- A loading dose of IV theophylline.
- IV magnesium sulfate (50%, 0.2 mL/kg as infusion in 30 mL of one-fifth normal saline in 5% dextrose over 35 minutes) gives gratifying results. Magnesium sulfate acts both by anti-inflammatory and bronchodilator effect. Minor side-effects of this therapy include tingling, numbness, flushing, warmth, malaise, etc. Hypermagnesemia (serum magnesium 5 mg/L or 2.5 mmol/L) may manifest with hyporeflexia, hypotension and drowsiness. Severe hypermagnesemia (serum magnesium 12–15 mEq/L or 6–7.5 mmol/L) may cause respiratory depression, coma and even death.

Absence of improvement despite all this is an indication for mechanical ventilation. Factors contributing to poor response and warranting attention include:

- Coexisting acidosis
- Dyselectrolytemia
- Superadded infection.

Table 26.6: Clinical respiratory scoring system

Criteria	Scores		
	0	1	2
PaO ₂ mmHg (torr) or	70–100	Under 70 in room air	Under 70 in 40% O ₂
Cyanosis	Nil	in room air	in 40% O ₂
Inspiratory breath sounds	Normal	Unequal	Decreased or absent
Use of accessory muscles of respiration	Nil	Moderate	Marked
Expiratory wheeze	Nil	Moderate or nil because of poor air exchange	Absent
Mental status (Cerebral function)	Normal	Depressed	Coma or agitated

Additional Measures

- Mild sedation with phenobarbital (morphine is contraindicated) or tranquilizers like chlorpromazine and chlorthalidone to allay anxiety and emotional stress.
- Expectorants to remove excessive secretions.
- Antibiotics in the presence of infection which is frequent.
- Maintenance of fluid and electrolyte balance; correction of metabolic acidosis (if documented) with soda bicarbonate.

Management of Status Asthmaticus

Status asthmaticus is defined as a state in which an asthmatic patient continues to suffer from dyspnea in spite of administration of sympathomimetic agents as well as aminophylline/theophylline. He is a candidate for receiving treatment in an intensive care unit (ICU). Employing the respiratory scoring system (Table 26.6), the severity of his problem should be graded as below:

- **Score 0–4:** No immediate danger
- **Score 5–6:** Impending respiratory failure
- **Score 7 or above:** Respiratory failure.

Respiratory score is recorded at the very outset and then monitored at regular intervals. At score 5–6 or above, all arrangements for assisted ventilation should be kept ready.

Failure of maximal medical therapy is an indication for considering extracorporeal membrane oxygenation (ECMO) which may prove life-saving even in gravely ill subjects.

Management of Persistent Asthma**Management of asthma in between acute exacerbations:**

- During the period in between attacks, attempts should be made to detect the offending allergen, to avoid this and, if possible, to hyposensitize the patient.
- **Asthma preventers** (ketotifen, cromoglycate, steroids) may be used in chronic asthma to prevent acute exacerbation.
- Since infection is an important excitatory factor, it should be controlled at the earliest opportunity. Also,

Box 26.14 Pharmacological management of different grades of asthma

- **Mild intermittent (episodic) asthma:** Oral or inhaled salbutamol or terbutaline as and when required
- **Mild persistent asthma:** Inhaled short-acting β_2 agonists plus inhaled steroids
- **Moderate persistent asthma**
- **Severe persistent asthma:** Inhalation steroids plus long-acting β -agonist and/or slow release theophylline. Add on therapy with montelukast yields better control. Poor control is an indication for oral steroids (low dose alternate day prednisolone).

seats of infection, i.e. tonsils, adenoids, nasal polyp, etc. should be removed.

- Physiotherapy regarding breathing and postural exercises gives gratifying results.
- Reassurance to an emotionally disturbed child is very important. He may have to attend a child guidance clinic regularly.
- A change of environment may remove the offending allergen and also the functional stimuli.
- Among the recent developments in asthma rank, introduction of drugs that block the synthesis of leukotrienes, the mediators secreted by inflammatory cells, namely:
 - **LTD4 antagonists:** Zafirlukast, pobilukast, pranlukast, tomelukast, verlukast available under the trade name **Accolate** as 20 mg tablets.
 - **5-Lipoxygenase inhibitors:** Zileuton, available under the trade name **Zyflo** and **Leutrol** as 60 mg tablets.
 - **Montelukast** available as 5–10 mg tablets is awaiting formal approval.
 - **Methotrexate** is of value in reducing the dose of steroids in severe chronic steroid-dependent asthma. Box 26.14 presents grading of asthma and bronchodilator therapy in between attacks.

Education of Asthma Child's Parents

This should be on the following lines:

- Imparting knowledge and understanding of asthma as a lifelong disease in which, with proper treatment, active and normal life is workable.
- Avoidance of triggers, such as dust, smoke, any known or suspected allergen, such as white of egg.
- Adverse drug reactions (ADRs) of medication prescribed.
- Maintenance of record of child's symptoms indicating improvement or deterioration so that necessary changes in therapy can be made.
- Handling and interpretation of peak flow meter.

TUBERCULOSIS

Tuberculosis continues to be a common pediatric problem in the developing countries like India, particularly in the changed scenario following the onslaught of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS). Among the giant

446 killers of children in these regions, it ranks high. Besides considerable mortality, this public health problem of a great magnitude causes much ill-health. According to an National Institute for Research in Tuberculosis (NIRT), a permanent institute under the Indian Council of Medical Research (ICMR) survey, the incidence of tuberculosis in India is 1 in 50. This figure is close to those reported from other developing countries, such as Bangladesh, Pakistan, Malaysia, Indonesia, Sri Lanka, Nepal and United Arab Republic.

About 15–20% of pediatric beds in north India are occupied by infants and children suffering primarily from tuberculosis or tuberculosis in addition to another major entity like gross malnutrition. No other chronic infection of childhood comes anywhere close to this figure. Even in the pediatric outpatient departments, some 5–8% attendance is accounted by tuberculosis. With the advent of HIV infection, a definite predisposing factor for tuberculosis, the incidence of tuberculosis is likely to show a remarkable rise in the years ahead.

Etiopathogenesis

A child is infected by the bacilli from an open case of tuberculosis, usually an adult. The most common site is the lung, though lymph nodes, tonsils, skin, intestine, etc. may be the other possible locations for the primary infection.

About 2–10 weeks (average 6 weeks) after this primary infection, many viable bacilli are transported to the regional lymph glands. There is an exudative reaction locally. This may result in caseation in the gland.

The original focus of infection develops an accumulation of polymorphs. This is followed by epithelioid cell formation. Finally, there results a typical tubercle formation with its surrounding layer of mononuclear leukocytes and occasional giant cells. This is what has been described as the Ghon focus. It is about a centimeter in diameter and, together with lymphatic drainage of the area and regional lymph glands, is termed as the **primary complex** (Fig. 26.15). This focus usually shows slow healing with calcification and, sometimes, fibrosis. Primary complex is liable to **reactivation** following reinfection, especially about the time of puberty.

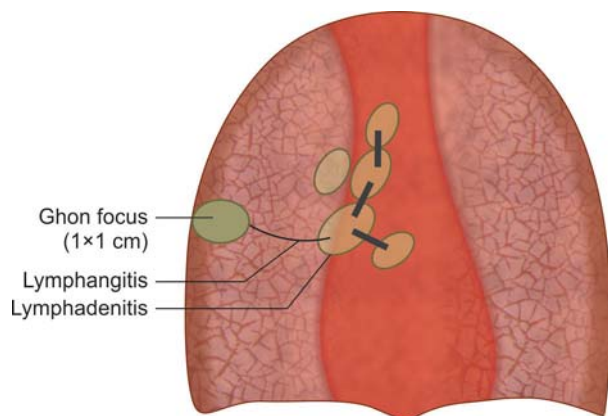


Fig. 26.15: Primary complex. The complex comprises of lymph nodes, lymphatics and Ghon focus.

Towards the end of the incubation period, the individual's allergy may be manifested in the form of fever, pleural reaction, erythema nodosum—elevated ovoid patches, 1–3 cm in diameter, over the legs, uncommon in Indian subjects, primarily because of the dark skin—phlyctenular conjunctivitis and positive tuberculin (Mantoux) test.

Congenital tuberculosis can occur from transplacental infection, or the fetus inhaling the bacilli from liquor amnii as a result of the tuberculous focus in the placenta. It is characterized by enlargement and caseation of the glands at porta hepatis and disseminated tubercles throughout the liver. This comprises the primary complex. In addition, tubercles are scattered through the lungs, spleen and other viscera. Brain and meninges may be similarly involved.

Fate of primary complex: The unresolved primary complex may meet the following fate:

- Local spread may cause:
 - Progressive pulmonary lesions like extended parenchymal involvement and pleural effusion.
 - Bronchial compression resulting in collapse or obstructive emphysema.
 - Bronchial erosion resulting in spread of infection to various parts of the lung, the so-called segmental or endobronchial tuberculosis.
- Hematogenous spread occurs owing to the proximity of a minute lesion to the intima of a blood vessel or rupture of a caseous gland into a large vein. Blood dissemination may lead to extensive miliary mottling of the lung (miliary tuberculosis), involvement of brain (meningitis and tuberculoma), spleen, liver, glands, peritoneum (peritonitis), bones and joints, kidneys and skin.

Clinical Types

Clinical picture is variable. Of the various types, 41% are intrathoracic with a mortality of nearly 5% and 28% are CNS tuberculosis with as high a mortality as 30–50%. Other forms are less frequent.

Primary Focus

Usually there are no manifestations, especially in infants and young children. This has earned it the name **silent primary**, which is, however, liable to get flared up by a subsequent attack of whooping cough or measles.

In older children, primary focus may cause vague symptoms, like malaise, fatigue, anorexia, weight loss, failure to thrive and low-grade fever. This is generally overlooked. A recent Mantoux conversion and routine X-ray examination of the chest often clinch the diagnosis.

Hilar Lymphadenitis

It is an important feature of primary complex. Cough, fever and weight loss are its common symptoms. It is usually impossible to detect it by mere clinical examination. Radiology and positive tuberculin test often point to its presence. At times, paratracheal adenitis may produce

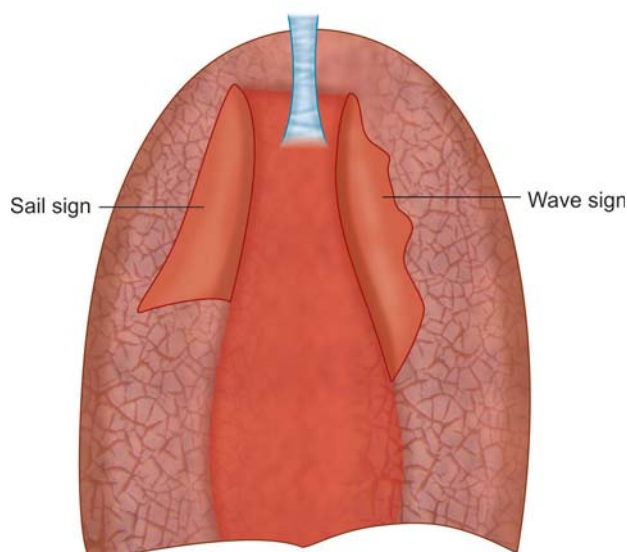


Fig. 26.16: Widened superior mediastinum. Sketch of the X-ray showing shadow produced by the enlarged thymus. Note the **sail sign** on the right and **wave sign** (due to indentation of ribs) on the left. This is an important differential diagnosis in shadow produced by hilar tuberculous adenitis.

marked widening of the superior mediastinum in an X-ray film (Fig. 26.16). It should be differentiated from shadow produced by thymus and glandular enlargement from a lymphoma or leukemias.

Segmental Lesions

Here signs and symptoms will depend on the extent of progressive primary lesion and the type of segmental lesion produced as a result of bronchial compression or erosion. Radiologically, it is difficult to differentiate segmental lesion of tuberculosis from nontuberculous collapse/consolidation, or bronchiectasis. The presumed nontuberculous lung lesions that have failed to resolve despite adequate antibiotics over a sufficient length of time need re-evaluation. This may be tuberculous.

Pleural Effusion

It is supposed to result from discharge of caseous material of a peripheral (subpleural) primary focus or enlarged regional lymph node. About 5–10% of children with pulmonary tuberculosis have pleural effusion. A vast majority of the patients are beyond 5 years of age.

Miliary Tuberculosis

It is the result of hematogenous dissemination and is characterized by extensive miliary mottling of lungs and involvement of spleen, liver and other tissues. CNS tuberculosis is a frequent accompaniment.

Its onset is usually insidious but may be sudden. High fever, malaise, night sweats, growth failure and anemia are the common manifestations. Cough is present in some cases. Hepatosplenomegaly is usually associated. Chest signs may be in the form of a few crepitations or may be absolutely absent. This happens in spite of marked toxemia.

X-ray chest is characteristic, demonstrating multiple minute dots which may blend. This has been described

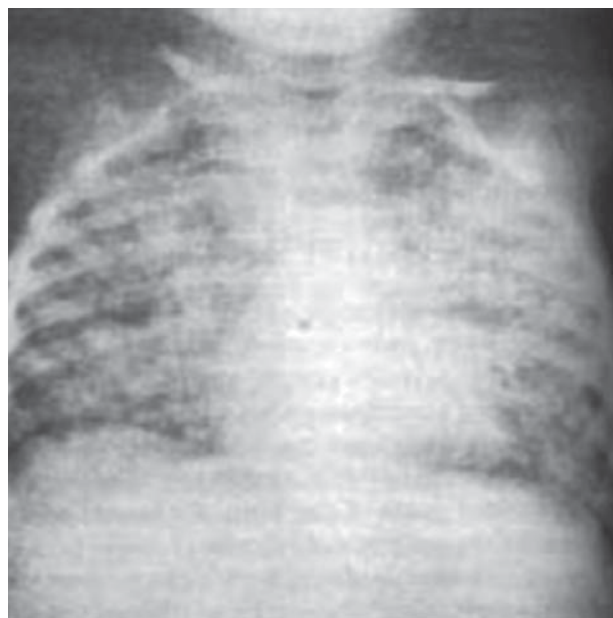


Fig. 26.17: Miliary tuberculosis. Note the snowstorm appearance as a result of multiple minute dots which tend to blend. Differential diagnosis includes staphylococcal pneumonia and tropical eosinophilia.

as snow-storm appearance (Fig. 26.17). The differential diagnosis is usually from staphylococcal pneumonia and tropical eosinophilia. Loeffler syndrome, histoplasmosis, whooping cough and hemosiderosis may also produce similar picture. Tuberculin test is generally negative and is, therefore, not reliable in miliary tuberculosis. BCG test is often positive. Almost half of the infants with miliary tuberculosis die.

Central Nervous System Tuberculosis

It is the most dangerous of all the forms of tuberculosis. As in case of miliary tuberculosis, its peak incidence occurs 6 months to 1 year after the primary infection. CNS tuberculosis is described in detail in Chapter 28 (Pediatric Neurology).

Superficial Tuberculous Lymphadenitis

It is quite a common problem in our country, constituting around 20% of the cases of tuberculosis. Cervical glands are most frequently involved followed by axillary glands. Generalized adenitis is less frequent. To begin with, the glands are discrete and mobile but soon become matted and adherent to the overlying skin. The gland may caseate and discharge its necrotic material into the skin. The result is an exudative crusted skin lesion. This is called scrofuloderma. In case of doubt regarding the tuberculous etiology of the superficial glands, fine needle aspiration cytology (FNAC) or a gland biopsy must be done.

Abdominal Tuberculosis

It is relatively uncommon. Three forms are usually described, which are as follows:

1. **Tuberculous mesenteric** (glandular involvement).
2. **Peritonitis** which is of two types:

- 448
- i. **Ascitic abdominal tuberculosis** is characterized by massive ascites in a child who is otherwise emaciated.
 - ii. **Plastic abdominal tuberculosis** is characterized by chronic diarrhea, often alternating with constipation, chronic abdominal pain and growth failure.
 3. **Intestinal tuberculosis** in which epithelial ulceration, resulting in chronic diarrhea, is the main presenting feature.

Abdominal tuberculosis is usually secondary to primary focus in the lungs or elsewhere in the body. The diagnosis often presents difficulties. It is usually made on clinical grounds. The bacilli are infrequently demonstrable in ascitic fluid. Plain X-ray abdomen may reveal just calcified glands.

Skeletal Tuberculosis

Tuberculosis of bones and joints is almost always a late result of hematogenous spread from the primary complex in the lung. The common sites are spine (Figs 26.18 and 26.19), hip and knee joints. Tuberculosis of fingers and toes (dactylitis) also occurs. The manifestations of skeletal tuberculosis are generally local. Besides other measures, radiology of the affected part is a **must** for diagnosis.

Renal Tuberculosis

It is another late manifestation of hematogenous dissemination, taking 4–5 or even more years after the primary infection. Frequency of micturition, dysuria, sterile pyuria or painless hematuria may be the only manifestations. Obstructive uropathy due to involvement of renal pelvis and ureter may cause hydronephrosis.

Skin Tuberculosis

This may be in the form of:

- Erythema nodosum which occurs as a hypersensitivity response to the bacilli towards the end of the incubation period.



Fig. 26.18: Psoas abscess. Radiologic survey revealed caries of the lumbar spine. BCG diagnostic test was strongly positive (25 × 25 mm) after 48 hours.



Fig. 26.19: Caries of spine. Note the remarkable deformities of the dorsolumbar spine.

- Tuberculous ulcers are characterized by undermined edges (Fig. 26.20).
- Scrofuloderma is the involvement of skin overlying caseous lymph glands. It consists of oval ulcers with undermined edge and flabby granulation tissue at the base. Extensive skin lesions may result.
- Tuberculoides are tiny papules with concave surface. They may be multiple and occasionally as large as a pea. They slowly heal. A whitish scar is usually left.
- Lupus vulgaris is the rarest among the tuberculous skin lesions seen in children. It consists of small pinhead papules that enlarge and blend to form tubercles. The progression is slow but may cause disfigurement. Upper lip is the most common site.



Fig. 26.20: Tuberculous ulcers with undermined edges. There was significant enlargement of regional lymph nodes. The cause appeared to be direct inoculation of tuberculous bacilli into skin.



Fig. 26.21: Extensive cavitational tuberculosis in an adolescent.

Chronic Pulmonary Tuberculosis

A healed primary complex may get **reactivated** as a result of another infection or some precipitating factor like measles or whooping cough. This causes adult type of tuberculosis, the so-called reinfection or chronic pulmonary tuberculosis or phthisis (Fig. 26.21). It shows maximum incidence in adolescent girls. Unlike pulmonary lesions of other forms of tuberculosis in pediatric practice, apical and infraclavicular sites are usual in this variety. Moreover, cavitation is more common and glandular involvement less remarkable.

Other Forms of Tuberculosis

Tuberculosis of pericardium, ears and eyes—in fact, almost any organ/part of the human body—occurs in areas where the disease has a high prevalence. Major differences between childhood and adult tuberculosis are given in Table 26.7.

Table 26.7: Childhood vs adult tuberculosis

Childhood tuberculosis	Adult tuberculosis
Primary infection from an open case or reinfection	Reactivation of healed focus
Site of parenchymal lesion	Usually apical (primary focus) usually peripheral due to sluggish circulation
Healing by calcification in most cases	Fibrosis
Glandular element dominates	Uncommon
Segmental lesions common	Uncommon, cavitation frequent
Generally noninfective	Generally infective
Hematogenous dissemination common	Uncommon

Diagnosis

A high index of suspicion is of considerable importance. Tuberculosis should be suspected in the presence of growth failure, malnutrition, pyrexia of unknown origin (PUO), prolonged cough, recurrent chest infections, painless lymphadenopathy, asthma, pleural effusion, pneumonia not responsive to antibiotics for pyogenic infections and unsatisfactory recovery from illnesses like typhoid, whooping cough or measles. In the wake of history of exposure to a known open case of tuberculosis in the family or the neighborhood, the child should be investigated for tuberculosis, especially if he is not already vaccinated with BCG.

Mantoux Test

- 0.1 mL (5 units) of glycerinated purified protein derivative (PPD)* is injected intradermally over the anterior aspect of the forearm. The extent of induration (not erythema) is read after 48, 72 and 96 hours respectively and classified as below:
- Under 5 mm diameter—negative reaction
- 5–10 mm diameter—doubtful reaction
- 10–20 mm diameter—positive reaction
- 20–30 mm diameter—moderate reaction
- 30–40 mm diameter—severe reaction.

Interpretation

Positive reaction (Fig. 26.22) reading, i.e. exceeding 10 mm, indicates the following:

- Bacillus Calmette–Guérin already given to the child
- Infection with the virulent bacilli from a case of tuberculosis in the undermentioned situations:
 - Under 2 years of age
 - Under 6 years of age, provided the child is exposed to a known case of tuberculosis
 - Recent conversion from negative to positive.



Fig. 26.22: Tuberculosis. Note the strongly positive tuberculin (Mantoux) and Bacillus Calmette–Guérin tests.

* Old tuberculin (OT) is best avoided in tropical areas. It deteriorates rapidly and has got to be used quickly after dilution.

450 The stronger the reaction, the more likely is the possibility of activity of tuberculosis. Thus, children used quickly after dilution with Mantoux reading of over 20 mm have high chances of a demonstrable pulmonary lesion.

- **False-negative reaction:** Due to depressed sensitivity, an individual may show false-negative tuberculin reaction, despite the presence of tuberculosis, in the following situations:

- Poor technique
- Incubation period
- Advanced tuberculosis, e.g. miliary tuberculosis, tuberculous meningitis, etc
- Convalescence from whooping cough or measles
- Steroid therapy

Bacillus Calmette–Guérin diagnostic test is no longer recommended.

- **Radiology:** Every child with suspected tuberculosis should have an X-ray chest. Radiologic appearances (hilar prominence, miliary tuberculosis, pleural effusion, calcification, segmental lesions, etc.) are helpful in arriving at the diagnosis, though these are seldom pathognomonic.

X-ray skull may reveal **silver-beaten** (also termed as **copper-beaten**) appearance, indicating raised intracranial tension, and/or calcification when tuberculoma is present. Depending on the affected part, such X-rays as those of bones, joints, abdomen, etc. may be required.

- **CT scan:** This may be of a great help in detecting tuberculoma, obstructive hydrocephalus, cerebral edema, infarction, basal exudates and fibrosis in CNS tuberculosis, as also in differential diagnosis of mediastinal and abdominal masses, skeletal and other local lesions, etc. It can also be of considerable help in follow-up. Pulmonary lesion missed by routine radiology of the lungs may be detected by CT scan.

- **Demonstration of bacilli:** Sputum, gastric lavage, laryngeal swab, pleural tap, cerebrospinal fluid (CSF), discharge from glands, etc. may be employed depending on the individual merits of a case, for smear (Ziehl-Neelsen method of staining), culture or guinea pig inoculation. The fluorescent staining with auramine and examination under a good fluorescent microscope is superior to the conventional Ziehl-Neelsen method as far as positivity, ease of detection and speed are concerned.

Since culture of the slow-growing tuberculous bacilli (on conventional Lowenstein-Jensen egg medium or newer, the Dubos Oleic acid-agar medium) takes some 6–12 weeks for primary isolation, slide chamber or radiorespiratory techniques may be employed for evidence of growth in 8–10 days and 3–4 days, respectively.

- **Serology:** Serological methods such as enzyme-linked immunosorbent assay (ELISA) and radioimmunoassay (RIA) have been proposed to detect antibodies to antigens of bacilli in such specimens as cerebrospinal

fluid (CSF) or urine. A rapid molecular test kit (Xpert MTB/RIF test) claims to detect *Mycobacterium tuberculosis* (including multi-drug-resistant (MDR) strains) in just 90 minutes. At present, such claims appear to be unfounded. Serological tests for rapid diagnosis of tuberculosis is therefore, not recommended. In fact, it stands banned in India.

- **Biochemistry:** Characteristic biochemical findings in CSF in TBM are elevation in proteins (slight to moderate) slight reduction in sugar, and marked reduction in chlorides in association with leukocytosis with predominance of lymphocytes.

Such body fluids as from joint cavity, pleural cavity and peritoneal cavity are characteristically straw-colored and exudates (proteins beyond 3 g%) with predominance of lymphocytes.

- **Fine needle aspiration cytology:** This simple diagnostic technique is now increasingly being employed and gives gratifying information.

- **Biopsy:** Histologic evidence of tuberculosis is often possible from liver biopsy, especially in disseminated (hematogenous) tuberculosis. Also, in doubtful superficial lymphadenopathy, a gland biopsy may be of much help. Biopsy may show a granuloma formation with giant cells and epithelioid cells and central caseation which is more characteristic of tuberculosis. Rarely, acid-fast bacilli (AFB) may be demonstrated in the biopsied material. Some workers have found bone marrow studies of distinct help in the diagnosis of tuberculosis.

- **Polymerase-chain reaction (PCR):** Based on amplification of mycobacterium tuberculosis-specific DNA sequences in clinical samples, PCR appears to be the most specific, rapid and sensitive diagnostic test. However, it is quite expensive and needs to be restricted to difficult cases and research studies only.

- **Supporting investigation:** High erythrocyte sedimentation rate (ESR), choroid tubercles, etc.

The foregoing was the broad outline for diagnosis of tuberculosis. It should be remembered that not all these procedures are to be carried out in each and every patient. As for example, gland biopsy need not be done in a child suffering from pleural effusion with bilateral hilar prominence and strongly positive tuberculin test. Likewise, there is no need to do lumbar puncture in a child with primary complex but nothing at all indicative of CNS involvement. On the other hand, certain cases will require investigations not mentioned above. Suspected cases of abdominal tuberculosis will, for instance, need radiology of abdomen.

Figures 26.23 and 26.24 present diagnostic approach for pediatric tuberculosis as per National guidelines. The salient recommendations are:

- All efforts should be made to demonstrate bacteriological evidence for the diagnosis of pediatric tuberculosis. In cases where sputum is not avail-

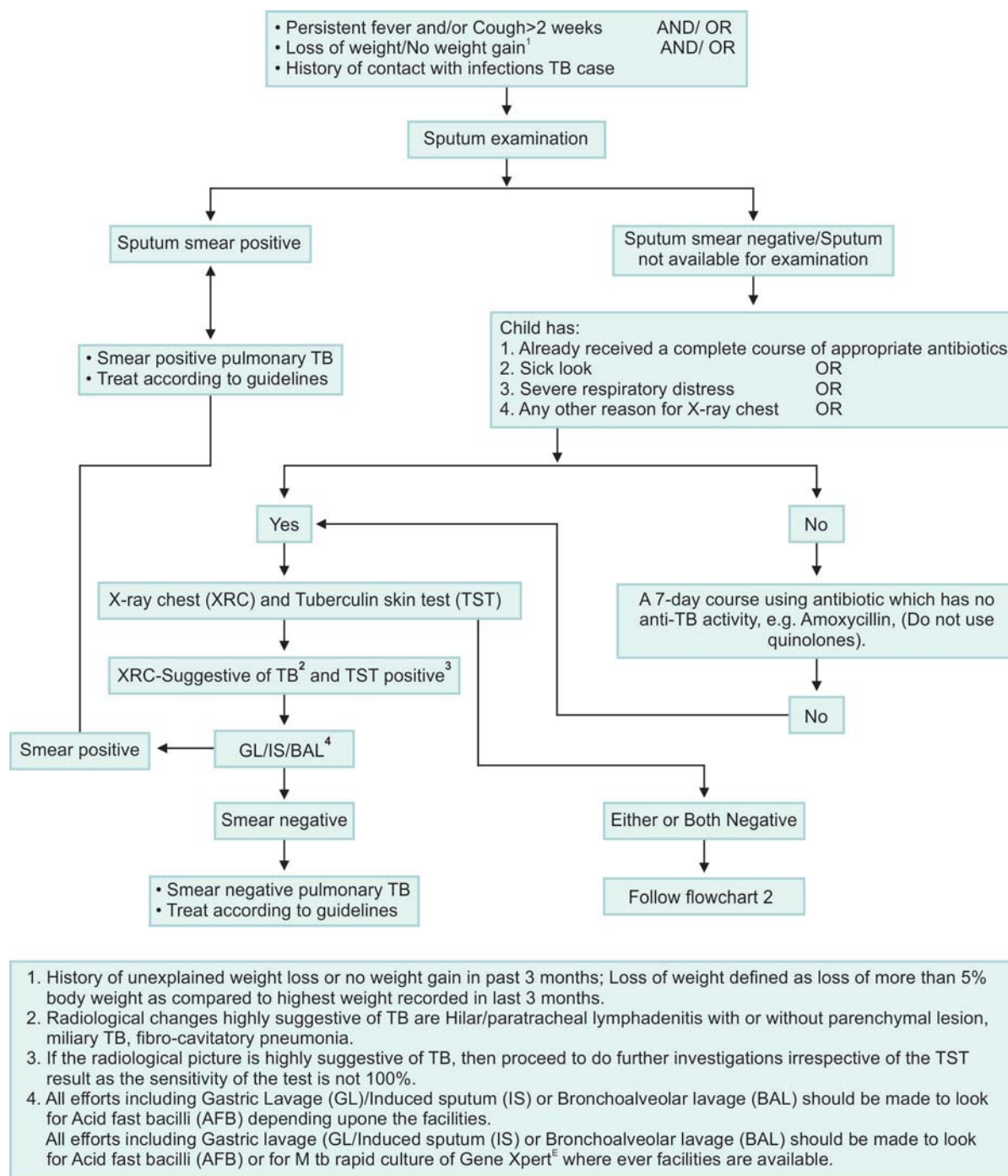


Fig. 26.23: Algorithm for diagnosis of pediatric tuberculosis.

able for examination or sputum microscopy fails to demonstrate AFB, alternative specimens (gastric lavage, induced sputum, bronchoalveolar lavage) should be collected, depending upon the feasibility, under the supervision of a pediatrician.

- A positive tuberculin skin test/Mantoux test was defined as an induration of 10 mm or more, measured 48–72 hours after intradermal injection with Tuberculin 2 TU (RT 23 or equivalent). In HIV cases the cut off is reduced to 5 mm or more of induration.
- There is no role for inaccurate/inconsistent diagnostics like serology (IgM, IgG, IgA antibodies

against MTB antigens), various in-house or nonvalidated commercial PCR tests and BCG test.

- There is no role of interferon-gamma release assays (IGRAS) in clinical practice for the diagnosis of TB.
- Loss of weight—often used as a clinical marker for the disease has been objectively defined as a loss of more than 5% of the highest weight recorded in the past 3 months.

Antituberculous Treatment

An ideal antituberculous drug needs to possess three characters, namely:

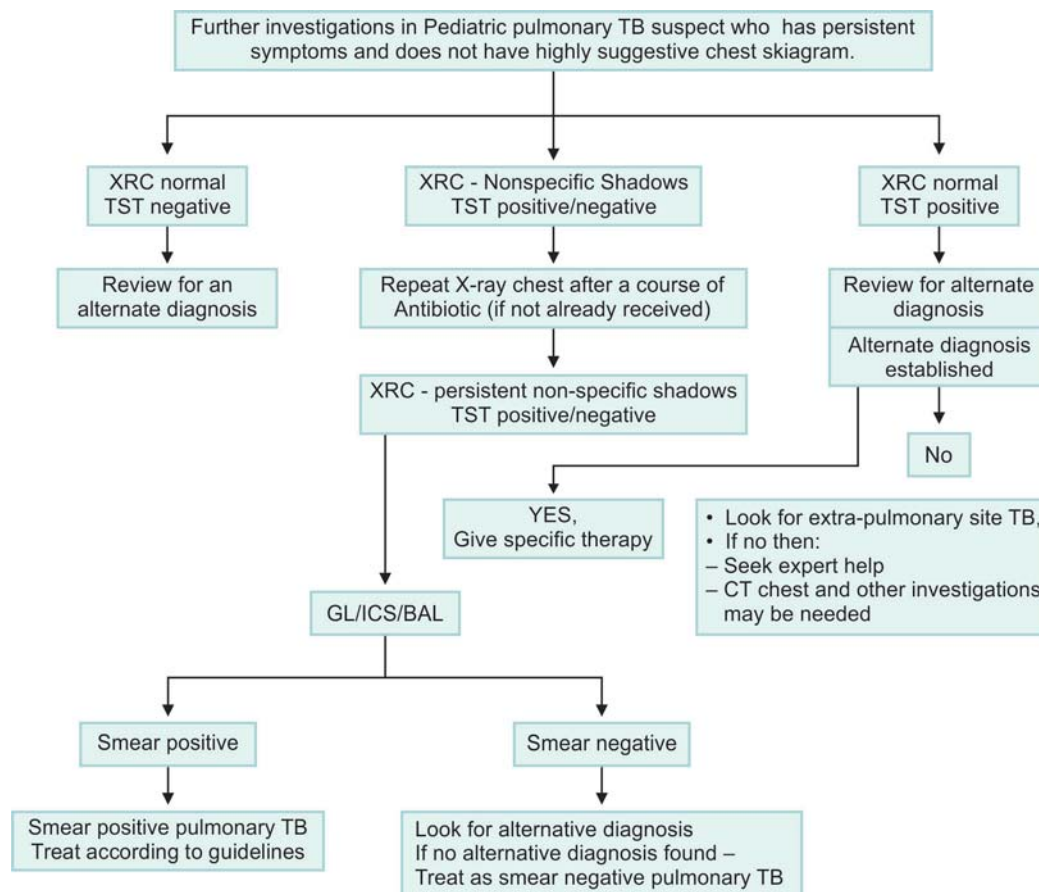


Fig. 26.24: Algorithm for diagnosis of pediatric tuberculosis in the event of suggestive manifestation but without highly suggestive chest X-ray (CXR).
 Abbreviations: ICS, intracellular staining; BAL, bronchoalveolar lavage; GL, gastric lavage; XRC, X-ray chest; TST, tuberculin skin test; CT, computed tomography.

1. Potent bactericidal activity against metabolically active bacilli.
2. Sterilizing activity against semidormant persisting bacilli
3. Potential to prevent emergence of resistant organisms throughout the period of chemotherapy.

An agent that possesses all these characteristics to sufficient degree is yet to be discovered. As of now, at least three antituberculous drugs must be given concomitantly, especially during the first 2 months, to safeguard against resistance. In all cases, therapy must be continued with at least 2 drugs over a period of several months.

- By **bactericidal action** is meant the speed at which viable bacilli disappear from the sputum, etc.—during the first few days of chemotherapy. Isoniazid is the most potent bactericidal antituberculous drug followed by rifampicin and ethambutol. Streptomycin, pyrazinamide and thiacetazone have minimal or no bactericidal action.
- **Sterilizing action** means elimination of subpopulation bacilli that are unresponsive to other drugs, Rifampicin has the potential to kill the semidormant or intermittently active bacilli during the short period when they are susceptible to chemotherapeutic assault. Pyrazinamide is effective in zones of acute inflammation and against quiescent bacilli within

macrophages. After the inflammatory process is over, it becomes less effective.

- **Inhibition of acquired resistance** means suppression of proliferation of mutants resistant to other drugs. Isoniazid and rifampicin both are known for their sustained inhibitory effect. Pyrazinamide and thiacetazone are less effective. Thiacetazone is employed to inhibit the emergence of isoniazid-resistant strains in subjects on long-term regimens.

Indications for Antituberculous Therapy

- All children with demonstrable active tuberculous lesions, e.g. progressive primary complex, pleural effusion, miliary tuberculosis, meningitis, etc.
- All children below 5 years of age having positive tuberculin/BCG test, provided BCG had not been already given to them.
- All children, whose tuberculin/BCG test has recently converted positive, provided BCG had not been given to them a few months back.
- All unprotected children (BCG not given) who are exposed to open cases of tuberculosis.

Categorization of Antituberculous Drugs

- **Group I:** First line drugs include isoniazid, rifampicin, streptomycin, pyrazinamide and ethambutol (Table 26.8). Majority of the patients respond well to these drugs.

Table 26.8: Salient features of recommended antituberculous drugs in children

Drug	Dosage	Advers drug reactions (ADRs)
Rifampicin	10–12 mg/kg/day (maximum 600 mg/day)	Hepatotoxicity, nausea, vomiting, hypersensitivity reactions, orange-red staining of saliva, sputum, sweat, urine and stools, gastrointestinal (GIT) upset, cramps, visual disorders, eosinophilia, thrombocytopenia.
Isoniazid	10 mg/kg/day (maximum 300 mg/day)	Hepatotoxicity, constipation, weight gain, euphoria (which may rarely worsen to psychosis), pellagra-like dermatosis, peripheral neuritis, convulsions.
Ethambutol	20–25 mg/kg (maximum 1500 mg/day)	Visual disturbances (optic neuritis), GIT upset, drowsiness, euphoria, swelling of tongue, hepatic and renal dysfunction, leukopenia, bone marrow depression, aggravation of grand mal attacks.
Pyrazinamide (PZA)	30–35 mg/kg/day (maximum 1500 mg/day)	Hepatotoxicity, nausea, vomiting, hyperuricemia/gout, anorexia nervosa, arthralgia, myalgia, rash, dysuria, sideroblastic anemia, rarely blood dyscrasias and photosensitivity.
Streptomycin	15 mg/kg/day (maximum 1 g/day)	Ototoxicity, nephrotoxicity, anaphylaxis, fever, rash urticaria, angioneurotic edema, eosinophilia, hemolytic anemia, blood dyscrasias, azotemia, muscle weakness, amblyopia.

- **Group II:** Second line drugs include cycloserine, ethionamide, para-aminosalicylate (PAS), kanamycin and capreomycin. Their indications are:
 - Cases resistant to first-line drugs and
 - Cases in whom first-line drugs cannot be employed because of adverse effects.
- **Group III:** Reserve drugs include quinolones (ciprofloxacin), amikacin, ampicillin and imipenem. These are indicated in drug-resistant cases.

Currently Recommended Antituberculous Regimens

Short-course chemotherapy (SCC), the standard current recommendations globally, is given in two phases, usually for 6 months:

1. **Intensive phase:** This phase comprises of administration of at 4 drugs for 2 months to get rid of the bacterial load and to prevent emergence of resistant strains of *Mycobacterium tuberculosis*.
2. **Continuation phase:** This phase comprises of administration of at least 2 drugs to complete the course, usually for a period of 4 months.

National guidelines for pediatric tuberculosis are listed in Table 26.9. These reconcile between global and earlier Revised National Tuberculosis Control Program (RNTCP) guidelines.

Intermittent Versus Daily Regimen

The intermittent therapy remains the mainstay of treating pediatric patients. However, among seriously ill admitted children or those with severe disseminated disease/neurotuberculosis, the likelihood of vomiting or nontolerance of oral drugs are high in the initial phase. Such, select group of seriously ill admitted patients can be given daily supervised therapy during their stay in the hospital using daily drug dosages. After discharge they should be taken on thrice weekly directly observed treatment (DOT) regimen (with suitable modification to thrice weekly dosages).

Newer Case Definitions

- **Failure to respond:** A case of pediatric tuberculosis who fails to have bacteriological conversion to negative

status or fails to respond clinically/or deteriorates after 12 weeks of compliant intensive phase shall be deemed to have failed response provided alternative diagnoses/reasons for nonresponse have been ruled out.

- **Relapse:** A case of pediatric tuberculosis declared cured/completed therapy in past and has (clinical or bacteriological) evidence of recurrence.
- **Treatment after default:** A case of pediatric tuberculosis who has taken treatment for at least 4 weeks and comes after interruption of treatment for 2 months or more and has active disease (clinical or bacteriological).

For programmatic purposes of reporting, all types of retreatment cases where bacteriological evidence could not be demonstrated, but decision to treat again was taken on clinical grounds would continue to be recorded and reported as others for surveillance purposes.

Treatment Regimens

Current guidelines recognize are only two treatment categories—one for treating **new cases** and another for treating **previously treated cases**, (Table 26.9).

- **Extending intensive and continuation phase**

- Children who show inadequate or no response (on smear or clinico-radiological basis) at 8 weeks of intensive phase should be given benefit of extension of IP for 1 more month.
- In patients with TBM, spinal TB, miliary/disseminated TB and osteoarticular TB, the continuation phase should be extended by 3 months making the total duration of treatment to a total of 9 months. A further extension may be done for 3 more months in continuation phase (making the total duration of treatment to 12 months) on a case to case basis in the event of delayed response and as per the discretion of the treating physician/pediatrician.

Tuberculosis Preventive Therapy

The currently recommended dose of INH for chemoprophylaxis is 10 mg/kg (instead of 5 mg/kg) administered daily for 6 months. Tuberculosis preventive therapy should be provided to:

Table 26.9: Treatment categories and regimens for childhood tuberculosis

Category of treatment	Type of patients	Tuberculosis treatment regimens	
		Intensive phase	Continuation phase
New cases	• New smear-positive pulmonary tuberculosis (PTB)	$2H_3R_3Z_3E_3^*$	$4H_3R_3$
	• New smear-negative PTB		
	• New extra-pulmonary TB		
Previously treated cases	• Relapse, failure to respond or treatment after default	$2S_3H_3R_3Z_3E_3 + 1H_3R_3Z_3E_3$	$5H_3R_3E_3$
	• Retreatment others		

H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol; S, streptomycin.

*The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week. Pulmonary tuberculosis refers to disease involving lung parenchyma. Extra pulmonary tuberculosis refers to disease involving sites other than lung parenchyma. If both pulmonary and extra pulmonary sites are affected, it will be considered as pulmonary for registration purposes. Extra pulmonary tuberculosis involving several sites should be defined by most severe site.

- **Smear positive:** Any sample (sputum, induced sputum, gastric lavage, bronchoalveolar lavage) positive for acid fast bacilli. **New case:** A patient who has had no previous ATT or for less than 4 weeks.
- **Relapse:** Patient declared cured/completed therapy in past and has evidence of recurrence. **Treatment after default:** A patient who has taken treatment for at least 4 weeks and comes after interruption of treatment for 2 months and has active disease.
- **Failure to respond:** A case of pediatric tuberculosis who fails to have bacteriological conversion to negative status or fails to respond clinically or deteriorates after 12 weeks of compliant intensive phase shall be deemed to have failed response, provided alternative diagnoses/reasons for nonresponse have been ruled out.
- **Others:** Cases who are smear negative or extra pulmonary but considered to have relapse, failure to respond or treatment after default or any other case which do not fit the above definitions. In patients with TBM on category I treatment, the 4 drugs used during the intensive phase can either be HRZE or HRZS. Ethambutol should be preferred in children.

Children who show poor or no response at 8 weeks of intensive phase may be given benefit of extension of intensive phase (IP) for 1 more month. In patients with TBM meningitis, spinal tuberculosis, miliary/disseminated tuberculosis and osteoarticular tuberculosis, the continuation phase should be extended by 3 months making the total duration of treatment to a total of 9 months. A further extension may be done for 3 more months in continuation phase (making the total duration of treatment to 12 months) on a case to case basis in case of delayed response and as per the discretion of the treating physician. Under Revised National Tuberculosis Program (RNTCP) all patients need to be covered under directly observed intermittent (thrice weekly) therapy.

The supervised therapy is considered as the most optimal treatment and is followed under RNTCP. It is important to ensure completion of treatment in every case put on treatment to prevent emergence of resistance, particularly to rifampicin. In the rare circumstances where a patient is given daily therapy, observation and completion of therapy remains as important. It is the duty of the prescriber to ensure appropriate and complete treatment in all cases.

- All asymptomatic contacts (under 6 years of age) of a smear positive case, after ruling out active disease and irrespective of their BCG, tuberculin skin test (TST) or nutritional status.
- Chemoprophylaxis is also recommended for all HIV infected children who either had a known exposure to an infectious tuberculosis case or are TST positive (>5 mm induration), but have no active disease.
- All TST positive children who are receiving immunosuppressive therapy (e.g. children with nephrotic syndrome, acute leukemia, etc.).
- A child born to mother who was diagnosed to have tuberculosis in pregnancy should receive prophylaxis for 6 months, provided congenital tuberculosis has been ruled out. BCG vaccination can be given at birth even if INH chemoprophylaxis is planned.

Problem of Drug Resistant Tuberculous Strains

Though a major roadblock in controlling tuberculosis, resistant mycobacterial strains are an infrequent problem in children. Box 26.15 lists the situations in which resistant tuberculous strains may be suspected.

Box 26.15

Situation where drug resistant tuberculosis needs to be suspected in children

- Poor response to antituberculous therapy (ATT) provided that the prescription and compliance are up to the mark as per current recommendations
- Good response in the beginning but later down-hill course provided that the prescription and compliance are up to the mark as per current recommendations
- Exposure to cases of drug-resistant tuberculosis.

RECURRENT RESPIRATORY INFECTION (Recurrent Chest Infection)

One of the common problems confronting a pediatrician is occurrence of frequent respiratory infection in children during the first 5 years of life (more so in infants and toddlers) when immunological defense is yet to reach adult level.

Definition

There is no universally-accepted definition of RRI as yet. Currently, RRI is arbitrarily defined as occurrence of:

- 7 or more episodes per year (mild-moderate illness like URTI).
- 2 or more episodes per year or 3 or more episodes over lifetime of a serious illness such as acute otitis media

Box 26.16**Various causes of recurrent respiratory infection**

- **Anatomical defects/postnasal drip:** Deviated nasal septum (DNS), adenoids, sinusitis.
- **Infections:** Tuberculosis, asthmatic bronchitis.
- **Allergic:** Bronchial asthma, tropical eosinophilia, Loeffler syndrome.
- **Genetic/chromosomal:** Down syndrome, cystic fibrosis, gargoylism.
- **Aspiration:** Gastroesophageal reflux disease (GERD), hiatal hernia, tracheoesophageal fistula, achalasia.
- **Immunodeficiency states:** Protein energy malnutrition (PEM).
- **Mechanical:** Foreign body, extrinsic compression of trachea or large bronchus by enlarged glands or heart.
- **Miscellaneous:** Congenital heart disease, especially left-to-right shunt, prematurity, parental smoking.

(AOM), pneumonia, etc. during the first 5 years of life. Some authorities specify different objective criteria for different infections, e.g.

- **Pneumonia:** 2 episodes within the same year, or 3 or more episodes over any time period in lifetime.
- **Acute otitis media (AOM):** Three episodes within 6 months, or four or more episodes within 1 year.

Etiology

Most of the etiological agents are viruses (RSV, influenza virus, parainfluenza virus, adenovirus) followed by bacteria (pneumococcus, GAS, *Hemophilus influenza* type B, *Moraxella catarrhalis*, *Mycoplasma pneumonia*). Box 26.16 lists the important condition that contribute/predispose to RRI.

Diagnosis**Clinical**

A good history and clinical examination is mandatory for arriving at a reasonable provisional diagnosis. The known causes of RRI should be kept in mind while doing so. Information about parental smoking may clinch the diagnosis in some intractable situations.

Investigative

In addition to the routine investigations, including CBP, the following investigations may be considered depending on individual merits of the case:

- Chest X-ray (CXR)
- Sinus X-ray for allergic rhinosinusitis
- Spirometry for asthma
- Sweat chloride test for cystic fibrosis
- 24-hours esophageal pH study for GERD
- Isotope mill scans.

Treatment/Prevention

Treatment is dictated by the etiological diagnosis:

- Preventive antibiotic therapy with amoxicillin cotrimoxazole, etc. for 3–6 months is indicated in select cases (e.g. 3 or more episodes in 6 months) but it should be judicious and rational
- **Nutritional interventions:** Improvement in nutritional status by dietary and other means

- Intravenous immunoglobulin (IVIG) in B cell immunodeficiency
- Respiratory syncytial virus (RSV) immunoglobulin
- Ribosomal immunotherapy
- Immunization—Hib, pneumococcal and influenza vaccines must be given. Growth retardation is an important sequel.

CYSTIC FIBROSIS

This genetic multisystem disorder of exocrine glands (mucus-producing glands in the body) is now being increasingly diagnosed in the Indian subcontinent. CF gene stands identified.

Etiopathogenesis

Chronic lung disease secondary to thick mucus blocking the passages is the most serious problem. Exocrine pancreatic insufficiency is responsible for severe mal digestion and mal absorption. Small intestinal function and histology, which is usually not affected early in disease, too suffers in advanced disease, causing yet more steatorrhea because of damage to intestinal mucosa from severe malnutrition per se.

Clinical Features

The dominant manifestations are in relation to lungs secondary to the congestion and block of the passages with thick secretions (Box 26.17). In addition, the child suffers from recurrent/chronic diarrhea with steatorrhea (secondary to pancreatic dysfunction) with failure to thrive despite good appetite and intake.

Diagnosis

Diagnosis is established by sweat chloride more than 60 mEq/L though DNA studies should be considered

Box 26.17**Pulmonary/respiratory manifestations of cystic fibrosis****Symptoms**

- Cough
- Nasal obstruction and rhinorrhea
- Recurrent pneumonia
- Extensive bronchiolitis
- Wheezing
- Exercise intolerance
- Shortness of breath
- Hemoptysis
- Cor pulmonale
- Respiratory failure

Signs

- Nasal polyp
- Increased anteroposterior diameter of chest
- Generalized hyper-resonance
- Scattered or localized coarse crepitations
- Digital clubbing
- Expiratory wheezes
- Cyanosis

Complications

- Atelectasis
- Pneumothorax
- Cor pulmonale.

456 the gold-standard now. Also, See Chapter 29 (Pediatric Gastroenterology).

Treatment

Pancreatic enzyme replacement therapy (PERT) is the mainstay of treatment. Attention to nutrition is important.

DROWNING AND NEAR DROWNING

Definition

The term, drowning, refers to submersion in water leading to death within 24 hours. When the subject manages to survive after successful resuscitation for 24 hours, no matter whether he dies or survives later, the term, ***near-drowning***, is used. If he dies later, the term, ***near-drowning with delayed death***, is applied.

Etiopathogenesis

A vast majority of the drowning are accidental, e.g. mishaps in bathtubs, swimming pools, ponds, lakes, streams, flooded excavations, etc. Aspiration, laryngospasm or breath-holding are responsible for most of the mortality. Whatever the operative factor, eventually hypoxemia is the common denominator. Hypoxemia is accompanied by varying degree of metabolic acidosis and transient hypercarbia.

- **Sea-water drowning** causes hypertonic water to get into the alveoli.
- **Fresh-water drowning** alters the surface tension properties of the **surfactant**.

Pulmonary insufficiency with intrapulmonary shunting and ventilation/perfusion mismatching are the features of both types of drowning. Pulmonary injury may be aggravated by concomitant aspiration of gastric contents. In a large majority of the cases, tissue hypoxia may cause persistent metabolic acidosis. In fact, anoxia and metabolic acidosis rather than electrolyte imbalance contribute to most deaths.

Clinical Features

Manifestations include tachycardia, bradycardia, cardiac arrest, pulmonary edema, hypothermia, arrhythmias including ventricular fibrillation, hypotension, and CNS dysfunction.

Treatment

It consists in providing:

- Immediate ventilation (mouth-to-mouth breathing, continuous positive airway pressure {CPAP}, intubation)
- Oxygenation
- Circulatory support (closed cardiac massage).
- Diuretics, bronchodilators and IV soda bicarbonate may be employed depending on merits of the case.
- Only maintenance fluids are normally needed.

There is no place for prophylactic use of antibiotics and/or steroids.

Sequelae

Serious neurologic sequelae may occur in some cases of near-drowning.

ACUTE RESPIRATORY DISTRESS SYNDROME

(Acute Lung Injury, Adult Respiratory Distress Syndrome)

Definition

Acute respiratory distress syndrome, is defined as non-cardiogenic pulmonary edema causing severe respiratory distress as a result of a diffuse lung injury. It is a critical and potentially fatal condition seen even in as young an infant as 1–2 weeks.

Etiopathogenesis

Acute respiratory distress syndrome (ARDS) is caused by a diffuse lung injury. A number of triggering factors, including shock, near-drowning, septicemia, injury, drug overdose, aspiration, inhalation injury and DIC have been incriminated.

Diffuse alveolar damage is the central lesion. The initial or exudative stage is characterized by pulmonary congestion and edema and lasts up to 72 hours. The subject may recover or pass on to the chronic or proliferative stage between 1st and 3rd week after injury and is characterized by an enhanced density of type II pneumocytes and fibroblasts. In due course, type II pneumocytes are transformed into type I pneumocytes and collagen is deposited by stimulation of fibroblasts. The eventual fibrotic stage follows after persistence of ARDS for over 3 weeks and is characterized by extensive fibrosis which makes gas exchange difficult.

Cardiorespiratory dysfunction with resultant severe hypoxemia is the most important physiological feature of ARDS. The existence of concurrent abnormalities in the surfactant system predisposes the lungs to develop atelectasis and edema formation.

Clinical Manifestations

Initially, there is only mild respiratory distress and hyperventilation. In the subsequent 4–24 hours, the subject develops hypoxemia and such manifestations as increasing respiratory distress with cyanosis and inspiratory crepitations (crackles). A large intrapulmonary shunt may be demonstrated at this point. Unless the subject receives supplemental oxygen or mechanical ventilation, increasing hypoxemia and hypercapnia prove fatal.

Laboratory Diagnosis

- Though evidence of pulmonary edema is available in the X-ray of chest (Fig. 26.26) sooner or later, more useful information is obtained from arterial blood gas analyses which shows a partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2) <50 mmHg or a fraction of inspired oxygen (FiO_2) of $>0.6\%$; a $\text{PaO}_2/$

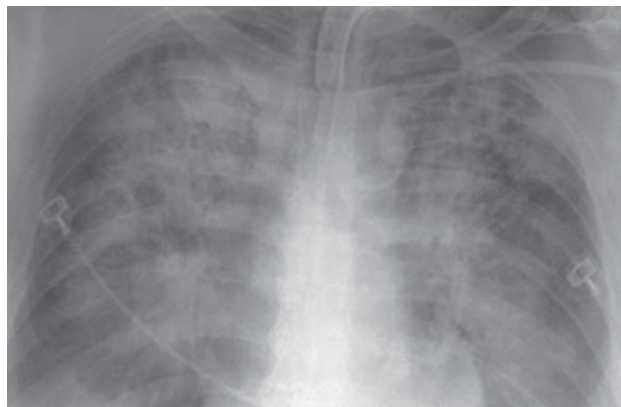


Fig. 26.26: Acute respiratory distress syndrome. Note the classical radiological changes in the form of a multitude of radicular opacities in nearly over all lung fields.

FIO_2 ratio of <200 correlates with a intrapulmonary shunt (QS/QT) (intrapulmonary shunt) of $>20\%$.

- CT scan shows that most of the pulmonary infiltrates are in the dependent (posterior) part of the lung.
- Pulmonary function tests show poor residual capacity and lung compliance.
- Pulmonary artery pressure and resistance show varying increase.

Treatment

The cornerstone of management of ARDS is delivery of sufficient oxygen with endotracheal intubation and mechanical ventilation, often with the help of positive-end expiratory pressure (PEEP). This essentially requires the facilities of the intensive care unit (ICU). **Newer therapies are:**

- Pressure-controlled ventilation with permissive hypercapnia
- High frequency ventilation including high frequency positive pressure ventilation, high frequency oscillation and high frequency jet ventilation
- Negative pressure ventilation/liquid ventilation
- Extracorporeal membrane oxygenation (ECMO)
- Exogenous surfactant replacement
- Inhaled nitric oxide
- Eicosanoids or their inhibitors
- Vasodilators
- Pentoxifylline
- Steroids (only in advanced stages)
- Lung transplant.

Complications

These include nosocomial infections, septicemia, severe barotrauma, compromised cardiac output, oxygen toxicity, progressive pulmonary fibrosis, multiple system organ failure including acute tubular necrosis, DIC, hepatic dysfunction, cardiomyopathy, gastrointestinal bleed and ileus.

Prognosis

Mortality is very high (50–75%) and is usually the result of initiating causative event, multisystem organ failure or septicemia. The survivors usually revert to preillness status within the following year. Long-term prognosis in pediatric survivors is better than in adult.

CHILDHOOD INTERSTITIAL LUNG DISEASE

Definition

Childhood interstitial lung disease (CILD) is defined as a heterogeneous group of rare and diffuse lung diseases characterized by the presence of diffuse infiltrates in chest X-rays as a result of scarring in between the air sacs, usually with impaired gas exchange.

Classification

- **Primary:** Idiopathic, predominantly of pulmonary origin
- **Secondary:** Secondary to systemic disorders like systemic lupus erythematosus (SLE), sarcoidosis, pulmonary glycogenesis, disorders of lung growth and development, etc.

Etiopathogenesis

The pathogenesis of interstitial lung disease (ILD) is linked to various stages of alveolar development and maturation in infants and to primary pathological changes around the alveolar septum with fibroblast proliferation in older children.

Clinical Features

About one-third cases of CILD are infants. Clinical features are often nonspecific. Manifestations include cough, breathlessness, fever, crackles, clubbing and rhonchi. Tachypnea, chest wall retraction, exercise limitation, frequent respiratory infections, unexplained fever, failure to thrive, tiring during feeding and weight loss.

Diagnosis

- Radiology of lungs
- Lung function tests
- Lung histopathology
- High resolution computed tomography (HRCT).

Prognosis

One-third cases die. Among those who survive, only one-half have disease-free survival. The outcome of children with ILD is dismal in terms of death/disease free survival with studies reporting death in as many as 30% children and disease free survival in only 50% of the patients.

458 ACUTE RESPIRATORY FAILURE

Definition

It is defined as a life-threatening disruption of the respiratory system that impairs its primary functions of delivering oxygen and removing carbon dioxide from the pulmonary capillary bed. There occurs overwhelming derangement in arterial blood gases and acid-base status.

Classification

It may be hypoxemic or hypercapnic:

- **Hypoxemic respiratory failure** is characterized by PaO_2 of <50 mm Hg with a normal or low PaCO_2 .
Examples: ARDS, noncardiogenic pulmonary edema, pneumonia, pulmonary hypertension.
- **Hypercapnic respiratory failure** is characterized by a $\text{PaCO}_2 >50$ mmHg.
Examples: Drug overdose, neuromuscular disease, chest wall abnormalities, severe airway disorders.

Clinical Features

Table 26.10 gives the manifestations of acute respiratory failure.

Complications

- Ventilator-induced lung injury.
- Ventilator-induced abdominal distention.
- Air leak syndromes.
- Pneumothorax.
- Pulmonary interstitial emphysema.
- Upper airway edema from tracheal intubation.

Investigations

- **Laboratory**
 - Arterial blood gas (ABG)
 - Serum electrolyte
 - Alveolar-arterial oxygen difference—A-a (DO_2)
 - $\text{PaO}_2/\text{FiO}_2$ ratio.
- **Imaging**
 - Chest X-ray (CXR)
 - Chest CT scan in refractory cases
 - Fluoroscopy (screening) for movements of diaphragm and dynamic obstructive lesions
 - Ventilation-perfusion (V/Q) scanning.
- **Investigative procedures**
 - Bronchoalveolar lavage
 - Lung biopsy.

Broad Line of Treatment

- Prone positioning
- Oxygen
- Bronchodilators in obstructive lung disease
- Steroids
- Noninvasive positive pressure ventilation (NPPV)
- Tracheal intubation, preferably with cuffed tubes
- Conventional mechanical and nonconventional modes of ventilation

Table 26.10: Manifestations of acute respiratory failure

Increased respiratory drive	Evidence of lung disease
<ul style="list-style-type: none"> Increased rate/depth of breathing Anxiety Breathlessness/dyspnea Retractions Accessory muscle use: <ul style="list-style-type: none"> Sternocleidomastoid Intercostal Alar nasae (nasal flaring) 	<ul style="list-style-type: none"> Wheezing/rhonchi/rales Retractions Suprasternal Intercostal Subcostal
Decreased respiratory drive	Evidence of respiratory muscle weakness
<ul style="list-style-type: none"> Decreased rate/depth of breathing Lethargy Confusion Snoring 	<ul style="list-style-type: none"> Chest wall paradox Shallow breathing Ineffective cough
Respiratory muscle fatigue	Hypercapnia
<ul style="list-style-type: none"> Paradoxic “see-saw” respirations Grunting Irregular/uncoordinated breathing 	<ul style="list-style-type: none"> Throbbing morning headaches Disrupted sleep Decreased level of consciousness
Hypoxemia	Evidence of loss of airway protective reflexes
<ul style="list-style-type: none"> Cyanosis Digital clubbing Increased pulmonary closure sound Failure to thrive 	<ul style="list-style-type: none"> Absent gag and cough reflexes Gurgling respirations
	Evidence of critical upper airway obstruction
	<ul style="list-style-type: none"> Stridor Droping, posture (leaning forward) Muffled/absent breath sounds

- Inhaled nitric oxide
- Exogenous surfactant
- Extracorporeal life support (ECLS).

Prognosis

It is grave in conditions with prolonged hypoxemia and irreversible disease like idiopathic pulmonary hypertension. In ARF associated with a chronic neuromuscular disease or thoracic deformity, prognosis can be fair.

SEVERE ACUTE RESPIRATORY SYNDROME

It is a viral respiratory disease of zoonotic origin caused by the severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) which is an RNA virus, involving only the respiratory system. Between November 2002 and July 2003, a large outbreak of SARS in southern China caused thousands of deaths, mainly from Hong Kong, Singapore, Vietnam, United States and Canada among other countries.

Unlike in adults (especially the elderly in whom it is a serious emergency illness), clinical profile in children is by and large mild. Most children have upper respiratory illness which may be ignored. In moderate respiratory illness (more often in older children and adolescents), fever, cough, shortness of breath or hypoxia is seen. In severe illness, in addition to the manifestations of moderate illness, bronchopneumonia with respiratory distress may complicate the clinical scenario. Mercifully,

thanks to endeavors of the WHO and allied agencies, SARS got eradicated in 2003 per se.

MIDDLE EAST RESPIRATORY SYNDROME

(Camel Flu)

Middle east respiratory syndrome (MERS) is a flu-like viral respiratory illness that is new to humans and originated

from middle-east. The causative virus is MERS-coronavirus (MERS-CoV). **459**

In children, symptoms include fever, cough, diarrhea, and shortness of breath. Disease is typically more severe in those with other health problems. It was first reported in Saudi Arabia in 2012 and has since spread to several other countries, including the United States.

Multiple Choice Questions

- All of the following are true in case of X-ray film in pulmonology, except:
 - PA view and sometime, lateral view as a routine
 - Decubitus film for pleural effusion
 - Oblique film for focus on hilar shadow and lung portion at the back of the heart
 - Lordotic film for superior mediastinum
 - Lateral neck film for upper airway obstruction around the level retropharynx, subglottis and supraglottis
- Spot the wrong observation:
 - Acute respiratory distress syndrome occurs only beyond first 6 months of life
 - Chest X-ray in bronchiolitis obliterans resembles that in miliary mottling
 - Pneumococcal pneumonia* accounts for 90% pneumonias in children
 - Recurrent pneumonia must raise suspicion of cystic fibrosis among other conditions
 - Pleural pain is characterized by accentuation on deep breathing and often radiation to shoulder or back
- All of the following entries about bronchial asthma are correct, except:
 - Children with severe bronchial asthma over a prolonged period may develop a barrel-shaped chest
 - A peak expiratory flow rate (PEFR) meter is very useful in the diagnosis of asthma
 - In refractory cases of bronchial asthma, intravenous magnesium sulfate may prove effective
 - Add-on therapy with montelukast only rarely improves the outcome in persistent asthma
 - Poor control in moderate-to-severe asthma is an indication for low dose oral steroids (prednisolone) given on alternate days
- Spot the wrong observation about pulmonary tuberculosis:
 - Primary complex consists of lymph nodes, lymphatics and Ghon focus
 - Sail sign and wave sign are suggestive of mediastinal widening
 - Snow-storm appearance in CXR is suggestive of miliary mottling-usually indicative of miliary tuberculosis
 - Neurotuberculosis is the most dangerous of all types of tuberculosis
- All of the following statements are correct, except:
 - Legionellosis is caused by a Gram-negative pathogen, *Legionella pneumophila*
 - In drowning, cause of death is always laryngospasm
 - DNA rather than sweat chloride test is the gold standard in diagnosis of cystic fibrosis
 - Differential diagnosis of wheezy chest includes gastroesophageal reflux
 - Neurotuberculosis is usually an indication for prednisolone for a few weeks

Answers

1. D 2. A 3. D 4. E 5. B

Clinical Problem-solving

Review 1

A 2-month-old infant presents with inspiratory stridor (intermittent) since the age of 15 days. The stridor shows worsening on crying and when he lies supine. He is otherwise well with a weight of 4.8 kg.

- What is most likely diagnosis?
- What could be the mechanism of its production?
- What is the therapeutic approach?
- What according to you should be the prognosis?

contd...

Review 2

A 2-year-old, suffering from moderate malnutrition with pyoderma develops increasing breathlessness, fever and painful left hip. Examination shows tachypnea with subcostal and intercostal retractions, dullness with increased vocal fremitus, resonance and bronchial breathing over left lower chest. There was inflammatory swelling over left hip joint. Among other investigations, X-rays of chest and left hip joint were requisitioned. Meanwhile, the resident started him on intravenous ampicillin.

1. What is your diagnose?
2. What is the most likely pathogen?
3. Is the resident right in starting ampicillin. What should be the better approach?
4. Is there any likely relationship?

Answers**Review 1**

1. Congenital laryngomalacia.
2. Aryepiglottic folds and other structures around the laryngeal aperture are thick and flabby, thereby causing narrowing of the laryngeal inlet during inspiration.
3. Reassurance.
4. Gradual decline in severity with complete resolution by 6–12 months age is usual in these infants.

Review 2

1. The clinical picture strongly suggests diagnosis of lobar pneumonia (consolidation) left lower lobe with septic arthritis left hip joint.
2. In view of presence of moderate malnutrition and pyoderma, there is very good chance of *Staphylococcal aureus* as the cause of consolidation.
3. In view of high incidence of resistant strains of *Staphylococcus aureus*, it is advisable to give cloxacillin together with ampicillin or amoxicillin.
4. Septic arthritis appears to be a complication of *Staphylococcal pneumonia* as a result of distant metastatic spread from the pneumatocele.

FURTHER READING

JOURNAL ARTICLES/BOOKS CHAPTERS

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An overwhelming proportion of cardiovascular diseases in children are congenital followed by rheumatic heart disease and systemic hypertension. Recent advances in understanding of pathophysiology, diagnostics medical and surgical therapeutics have considerably improved prognosis with survival into adulthood in some of the diseases which were until recently considered fatal.

EVALUATION OF A CARDIOVASCULAR CASE

An infant or a child with suspected cardiovascular disorder must be subjected to a good history and physical examination before taking recourse to investigative evaluation. The significance of such an evaluation cannot be overemphasized.

Clinical Work-up

- **History** should focus on cyanosis, squatting, fatigue, orthopnea, nocturnal dyspnea, feeding difficulty, sweating during feeding and chest pain. Attempt should be made to determine any history of presence of a generalized disorder affecting the heart as well. Any suggestion of a known congenital malformation syndrome, e.g. fetal alcohol syndrome (atrial septal defect {ASD}, ventricular septal defect {VSD}), VATER association (VSD, tetralogy of Fallot {TOF}, ASD, patent ductus arteriosus {PDA}). Down syndrome (endocardial cushion defects, VSD, ASD) needs to be taken notice of. In the family history, there may be suggestions of a generalized muscle disease (muscular dystrophy, dermatomyositis), prior congenital heart disease (CHD), or early coronary artery disease (familial hypercholesterolemia).
- **Physical examination** should target at assessing the growth and development of the child at the very outset. Presence of cyanosis, clubbing, edema, chest deformity, engorgement of neck veins, tachypnea and hepatomegaly needs to be specially observed. Pulse or cardiac rate and character of pulses provide valuable information. Blood pressure should preferably be recorded in the arms as well as in the legs. For this purpose, flush method is most feasible in restless infants. Cardiac examination must in particular be very careful, noting the presence of a precordial bulge, substernal thrust, apical heave or a hyperdynamic precordium, thrills (both systolic and diastolic), aortic bruits, etc.
- **Auscultation** of the precordium requires patience, first concentrating on the characteristics of the individual heart sounds and then on the murmurs.

Later, attention should also be focused on clicks.

Murmurs should be described as to their timing, intensity, pitch, area of highest intensity and transmission. Whether a particular murmur is just functional (innocent with no significance) or has a pathological origin (CHD) must be decided. This may need additional investigations such as electrocardiography (ECG), X-ray and/or echocardiography, etc. In certain cases, cardiac catheterization may be required, particularly as a part of preoperative evaluation.

Over 30% children may have a murmur without significant hemodynamic abnormalities. Typically, the so-called **innocent murmur** is heard in the age group 3–7 years, occurs during ejection, is musical and brief, is attenuated in the sitting position, and is intensified by pyrexia, excitement and exercise. As the child grows, such a murmur shows a tendency to be less well heard and may regress fully.

It is of help to apply the time-honored Nada's criteria for presence of heart disease in suspected cases (Table 27.1). Also, See Chapter 2 (Pediatric History-taking and {Clinical} Examination) for additional details.

Investigative Work-up

- **X-ray studies** are vital for cardiac size and shape pulmonary vascularity, pulmonary edema and accompanying lung and skeletal anomalies like dysplasias or abnormal number of ribs.
- **Cardiothoracic ratio** (Fig. 27.1) is the ratio of maximum cardiac width and the maximum chest width in a midinspiration posteroanterior film with patient in upright position. A ratio of more than (0.5) 50% usually indicates cardiac enlargement. This ratio is more dependable in later childhood rather than in

Table 27.1: Nada's criteria for presence of heart disease

Major	
•	Systolic murmur. Grade 3 or more, always pansystolic
•	Diastolic murmur
•	Cyanosis (primarily central)
•	CCF
Minor	
•	Systolic murmur, less than Grade 3
•	Abnormal second heart sound
•	Abnormal ECG
•	Abnormal X-ray
•	Abnormal blood pressure.

Abbreviations: ECG, electrocardiography; CCF, congestive cardiac failure.

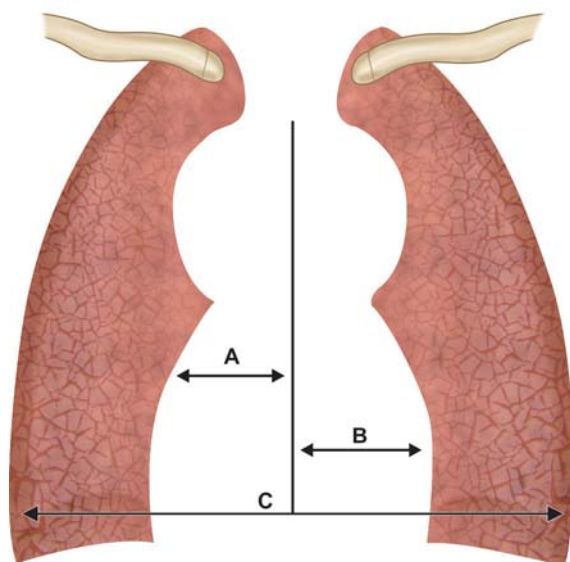


Fig. 27.1: Cardiothoracic ratio $\left(\frac{A+B}{C}\right)$ upto 0.5 (normal). In children, a ratio over 0.6 denotes cardiomegaly.

infancy. Even in later years, while interpreting this index, it needs to be ensured that thymic image or structural abnormalities of the thoracic cage such as pectus excavatum are not present.

- **Right border** of the cardiac shadow consists of (from above downward) superior vena cava, ascending aorta and right atrium.
- **Left border** of the cardiac shadow consists of (from above downward) aortic knob, main and left pulmonary arteries and left ventricle.
- **Enlargement** of cardiac chambers or major arteries and veins is indicated by prominences of the areas of their outlines on the chest film.
- **Pulmonary vascularity** is indicated by intrapulmonary shadows. Increased vascularity (overcirculation) is seen in left-to-right shunt whereas decreased vascularity (undercirculation) in right-to-left shunt. Since esophagus lies in the proximity of great vessels, esophagogram and screening (fluoroscopy), using barium, is of value in delineating these structures in selected situations such as coarctation of aorta and vascular ring.
- **Electrocardiography** is a vital investigation for demonstrating anatomical and hemodynamic changes, mainly in QRS and T wave morphology. What is needed in pediatric practice is a 13-lead ECG, including lead V3R or V4R, the latter being a must for determining right ventricular hypertrophy (RVH). Tall, narrow and spiked P waves (taller than 2.5 mm), resulting from right atrial hypertrophy, are seen in congenital pulmonary stenosis, Ebstein anomaly of tricuspid valve, tricuspid atresia, cor pulmonale, and sometimes thyrotoxicosis. Widened P waves, resulting from left atrial enlargement are encountered in VSD, communications between aorta and pulmonary circulation, and severe mitral stenosis. Flat P wave is a

feature of hyperkalemia. Right ventricular hypertrophy is denoted by:

- A QR pattern in right ventricular surface leads
- A positive T wave in leads V3–4R through V3 after first 48 hours of life
- A monophasic R wave in V3–4R and/or V1
- rsR, in right precordial leads
- Age-related voltage criteria in V3–4R and V1 (R), and/or V6–7(S)
- Significant right axis deviation, over 120 degrees
- A complete reversal of the normal adult precordial RS pattern
- Right atrial enlargement.

Left ventricular hypertrophy (LVH) is denoted by—(1) depression of the ST segment and inversion of T waves and left precordial surface leads; a left ventricular strain pattern; (2) increase in magnitude of initial forces to the right, meaning Q in left precordial leads, (3) voltage criteria in V3R and V1(S) and/or V6R. QT interval, varying with the cardiac rate, is prolonged in subjects at risk of ventricular arrhythmias and sudden death, e.g. Jervell and Lange-Nielsen syndrome with hearing loss, Romano Ward syndrome, etc. ST segment elevation is seen in normal adolescents, generalized pericarditis, superficial epicardial involvement, etc. Its depression is a feature of digitalis therapy, myocardial damage as in anemia, carbon monoxide poisoning, endocardial fibroelastosis, aberrant origin of left coronary artery from pulmonary artery, mucopolysaccharidosis, glycogen storage disease and myocardial tumors.

T wave inversion is a feature of any carditis. In hyperkalemia, T wave is tent-shaped and of high voltage. Hypothyroidism, on the other hand, leads to flat or inverted T wave and generalized low voltage. Complete bundle branch block is either congenital or a sequelae of open heart surgery. Left bundle branch block is either congenital or secondary to cardiomyopathy.

- **Echocardiography** is a revolutionary tool in the evaluation of congenital and acquired cardiac disease. M-mode echocardiography aims at identifying the motion of intracardiac structures like opening and closing of valves, and movement of septa, anatomy of valves and presence of endocardial vegetations exceeding 2–3 mm.
 - **Two-dimensional echocardiography** enables imaging the contracting heart by means of various views. It is a better technique, providing more realistic image of cardiac structures.
 - **Doppler echocardiography** identifies flow instead of morphology in cardiac chambers and vascular chambers. Abnormalities in blood flow in CHD are identified by the directional quality of Doppler. Color Doppler permits better evaluation of intracardiac shunts and valvular insufficiency.
 - **Transesophageal echocardiography** is a yet more sensitive imaging technique that can identify very small lesions such as vegetations in endocarditis.
- **Magnetic resonance imaging (MRI)** is of immense value in diagnosis and management of CHD. Cine MRI

permits acquisition of images in many tomographic planes at different phases of the cardiac cycle. Magnetic resonance spectroscopy allows demonstration of relative concentrations of high-energy metabolites (adenosine diphosphate, adenosine triphosphate, inorganic phosphate and phosphocreatine) within myocardium.

- **Radionuclide angiography** is employed to identify and quantify shunts and analyze distribution of blood to each lung.
- **Gated blood pool scanning** is employed to calculate the hemodynamic measurements, quantify valvular regurgitation and identify regional wall motion abnormalities.
- **Thallium imaging** is employed to evaluate perfusion of cardiac muscle.
- **Cardiac catheterization**, an important tool in the diagnosis of CHD, must only be limited to children, in whom the information obtained from echocardiography, including Doppler technique, and radionuclide studies, remains insufficient and the patient is a serious candidate for cardiac surgery. With this technique, different chambers of the heart are reached along with great vessels and veins. Blood samples are obtained for measuring oxygen saturation. Also, pressures are measured, and contrast and indicator materials injected if warranted. A noteworthy practical difficulty with this technique is that it has to be performed with the subject in a basal state. Else, calculations of hemodynamic measurements, say cardiac output, pulmonary and systemic resistance, and shunt ratios, are distorted. This prerequisite is often not workable in children. Cardiac catheterization is not without risks. The potential complications include hypothermia, acidemia, excess blood loss, severe arrhythmias, cardiac perforations, and intramyocardial injection of contrast material by mistake.
- **Angiocardiography** permits identification of specific cardiac abnormalities without interference from the superimposed shadows of normal chambers. It may be combination of photofluorography with a close-circuit television monitoring the fluoroscopic screen and allowing visualization of the cardiac silhouette and the catheter.
- **Interventional cardiology** aims at offering nonsurgical treatment of certain cardiac lesions that until recently needed open heart surgery, e.g. valvular pulmonary stenosis, aortic stenosis, PDA, secundum ASDs, etc.

FETAL CIRCULATION

It is vital to bear in mind the following features which are characteristic of fetal circulation and differentiate it from neonatal circulation:

- Shunts, both intracardiac and extracardiac, are present
- The two ventricles function in parallel instead of in series
- The right ventricle pumps blood against a resistance which is higher than that of the left ventricle

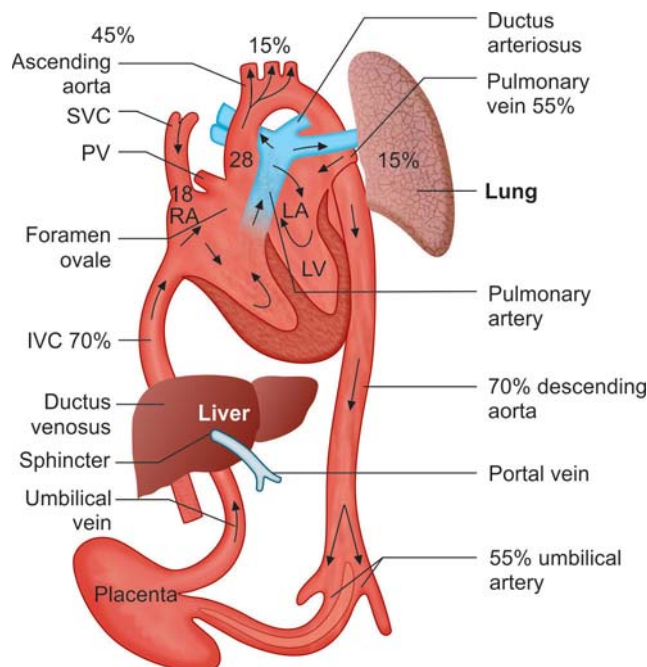


Fig. 27.2: Fetal circulation.

Abbreviations: SVC, superior vena cava; IVC, inferior vena cava; PV, pulmonary vein.

- The blood flow to the lungs is only a very minor proportion of right ventricular output
 - The lungs take oxygen from blood rather than supplying to it
 - The lungs continually secrete a fluid into the respiratory passages
 - The liver is the first organ to receive maternal substances like oxygen, glucose, and amino acids
 - The placenta is the principal site of gas exchange, excretion and acquisition of essential fetal chemicals
 - The placenta provides a low-resistance circuit
- Figure 27.2 depicts diagrammatic representation of fetal circulation, highlighting four sites of shunts, namely placenta, ductus venosus, foramen ovale and ductus arteriosus.

CIRCULATORY CHANGES AT BIRTH AND NEONATAL BLOOD CIRCULATION

At birth, with the cessation of placental circulation, major alterations in the circulation occur. These changes start immediately after birth and continue over a period of time thereafter.

- **Clamping of the umbilical cord** after the birth results in sudden increase in the systemic vascular resistance and consequent increase in the aortic blood pressure and left ventricular systemic pressure. The left ventricular diastolic pressure also tends to rise and increases the left atrial pressure. The sudden reduction in blood flow through the ductus venosus due to loss of placental circulation results in closure of ductus venosus. Exact mechanism by which the ductus venosus disappears is not known. The complete cessation of blood flow through the ductus venosus occurs by 7th postnatal day of life. The loss of placental flow also results in decrease

in volume of blood returning to the right atrium and consequent drop in the right atrial pressure. Increase in left atrial pressure results in left atrial pressure being higher than the right atrial pressure. This results in closure of foramen ovale. The approximation of septum primum with septum secundum contributes to the closure of foramen ovale. Though the functional closure of foramen ovale occurs quickly, the anatomical closure occurs over a period of months to year.

- **Sudden expansion of the lungs** with the first few breathes results in fall in pulmonary vascular resistance, which in turn results in increased pulmonary blood flow.

The reversal of pressures in the major blood vessels; aorta and pulmonary trunk, with higher aortic pressure leads to reversal of blood flow through the ductus arteriosus. Instead of flowing from pulmonary trunk to aorta, blood starts flowing in the reverse direction. This results in closure of ductus arteriosus. Though the exact mechanism is not known, the musculature of the ductus arteriosus has been found to be sensitive to change in oxygen saturation. Increased oxygen content in the blood causes constriction of the ductus musculature. In full-term neonates, the ductus arteriosus closes within 10–21 days. In preterm babies, the functional patency may be precipitated by various problems in immediate postnatal period (Box 27.1).

The pulmonary vascular resistance and right ventricle pressure continue to decline over next few weeks. Adult

relationship of pressure and resistance in the pulmonary and systemic circulation is established in approximately 2–3 weeks. All these changes result in the establishment of postnatal circulation. The blood returning from different parts of the body through superior and inferior vena cava reaches right atrium, courses through the right ventricle and through pulmonary vessels to the lungs for oxygenation. Oxygenated blood reaches left atrium, then to left ventricle and is pumped out by left ventricle through aorta and distributed to the body tissues.

HEART FAILURE (CONGESTIVE CARDIAC FAILURE)

Previously called congestive cardiac failure (CCF), heart failure is a common pediatric emergency. Since its etiology in infancy and childhood is at considerable variance with that of adults, the diagnosis as well as therapeutic approach has certain special features. By definition, **heart failure** means failure on the part of the heart to:

- Maintain an output necessary for the metabolic requirements of the body at rest or during stress (systolic failure).
- Failure to receive blood into the ventricles during diastole (diastolic failure).

Etiology*

It varies with age of the patient (Table 27.2).

Clinical Features

■ Infants

- Feeding difficulty
- Poor weight gain
- Irritability/excessive crying
- Excessive perspiration
- Wheezing
- Noisy labored breathing/tachypnea
- Hepatomegaly
- Cardiomegaly
- Tachycardia
- Gallop rhythm
- Edema, usually involving eyes, sacrum, legs and feet.

Box 27.1

Postnatal closure of important communications of fetal circulation

- **Ductus venosus:** The sudden reduction in blood flow through the ductus venosus due to loss of placental circulation results in closure of ductus venosus. The complete cessation of blood flow through the ductus venosus occurs by 7th postnatal day of life.
- **Foramen ovale:** Increase in left atrial pressure higher than the right atrial pressure results in closure of foramen ovale. The functional closure occurs immediately and anatomical closure occur in months to year.
- **Ductus arteriosus:** The reversal of blood flow through the ductus arteriosus from left to right side as a result of reversal of pressures in the major vessels results in closure of ductus arteriosus. In full term neonates, the ductus arteriosus closes within 10–21 days.

Table 27.2: Causes of CCF according to age

Age group	Conditions
Fetus	Severe anemia from fetomaternal transfusion or hemolysis, tachycardia (supraventricular or ventricular), complete heart block.
Newborn	Transposition of the great vessels, aortic atresia, coarctation of aorta, PDA, pulmonary stenosis/atresia, hypoplastic left heart syndrome.
1–2 months	Transposition of the great vessels, endocardial cushion defects, VSD, patent ductus arteriosus, aortic stenosis, coarctation of aorta, anomalous pulmonary venous connection.
3–6 months	Endocardial fibroelastosis, transposition of the great vessels, VSD, coarctation of aorta.
6–12 months	Endocardial fibroelastosis, VSD.
1–4 years	Carditis, anemia, nephrotic syndrome, acute nephritis, endocardial fibroelastosis, atrial or VSD.
4–12 years	All foregoing causes plus rheumatic heart and later disease.

Abbreviations: VSD, ventricular septal defect; CCF, congestive cardiac failure; PDA, patent ductus arteriosus.

* Overloading of circulation, as in overhydration, or severe chest infection, may cause heart failure at any age.

Box 27.2 Signs of heart failure (based on side)**Left-sided heart failure**

- Tachypnea
- Tachycardia
- Persistent cough (more so on lying down)
- Wheezing
- Hoarse cry
- Basal crepitations (sometime).

Right-sided heart failure

- Enlarged tender liver
- Facial puffiness
- Pedal edema may be delayed.

Both left and right-sided heart failure

- Cardiomegaly
- Poor peripheral pulses
- Cyanosis
- Third heart sound gallop.

■ **Children**

- Dyspnea at rest (orthopnea) or on exertion
- Tachycardia
- Raised jugular venous pressure
- Hepatomegaly
- Bilateral basal crepitations
- Edema
- Peripheral cyanosis
- Cardiomegaly
- Gallop rhythm.

Box 27.2 lists the signs of heart failure.

Investigations

- **Chest X-ray** assists in:
 - Assessing the cardiac size and pulmonary congestion
 - Excluding pulmonary etiology
 - Detecting CHD
- **Electrocardiography** may show nonspecific T and ST segment changes, tall P wave and specific patterns of congenital and acquired heart diseases.
- **Echocardiography** helps in assessing functional capacity of heart disease and diagnosis of infective endocarditis.
- **Other investigations** include hemogram, serum electrolytes, blood gas analysis, renal function and blood culture.

Management**Goals**

- Reducing cardiac work
- Increasing myocardial contractility
- Reducing cardiac size for improving its performance
- Treating underlying cause.

Measures for Reducing Cardiac Work

- **Bed rest:** The best position is that of propped up at an angle of 30–45°. Neonates are handled minimally. Most infants will need bed rest for a short period. Children with rheumatic heart disease should be kept in bed as long as rheumatic activity is there.
- **Sedation:** Restlessness and anxiety should be controlled with morphine (0.5 mg/kg subcutaneously). Alternatively,

a benzodiazepine (midazolam, diazepam), phenobarbital, chloral hydrate, or promethazine may be employed.

- **Oxygen:** It is usually given by a nasal catheter but, if facilities are available, the most comfortable and effective way of administering oxygen is plastic tent.
- **Antibiotics:** In neonates and infants, antibiotics should be given to control the coexisting infection/suspected infection that could have precipitated the failure by increasing cardiac work. In older children, antibiotics may be restricted to cases with evidence of infection.
- **Correction of anemia:** Blood transfusion (packed cells, 3–5 ml/kg), given carefully and slowly, leads to reduction in cardiac work. To prevent worsening of heart failure, frusemide (0.5–1 ml/kg IV) may be given just before the transfusion.
- **Vasodilators:** Vasodilators such as nitroglycerine and nitroprusside counter the existing vasoconstriction; thereby improving cardiac output and reducing work of the heart.

Measures for Increasing Cardiac Contractility by Inotropic Agents

- **Digitalization:** Digitalis continues to be the mainstay of management. The time-honored preparation, **digoxin**, is usually employed. One milliliter of a popular brand provides 0.05 mg of the agent. Table 27.3 outlines the dose for different ages.
 - One-half of the total calculated dose should be given stat. Divide the remaining half in two doses. Each half should be given at 8 hours intervals. Maintenance dose will be one-fourth to one-third of the total digitalizing dose. This is to be given either as a single dose or in two divided doses daily.
 - The above dosage is for oral administration of the drug. Parenteral dose should be about two-thirds of the oral dose.
 - Digoxin has been criticized on the ground that, being a catecholamine, it may further worsen the heart failure which is known for high catecholamine level and myocardial dysfunction. Nevertheless, in practice, it has been found useful and is recommended in all grades of heart failure. It improves the cardiac output, thereby indirectly reducing the systemic impedance. This unloads the ventricles, reducing their work.

Table 27.3: Total oral digitalizing dose of digoxin

Age groups	24-hour doses (mg/kg)
Newborn	
Full-term	0.05
Premature	0.04
1–12 months	0.08
1–3 year	0.06
>3 year	0.04

466 ■ **New Inotropic drugs**

- **Catecholamine group:** Dopamine, dobutamine
- **Non-catecholamine group:** Amrinone, milrinone, xamoterol, flosequinan

In practice, only dopamine and dobutamine are of proven value in pediatric heart failure.

Measures for Reducing Cardiac Size to Improve its Performance

- **Digoxin:** By reducing the heart size, it improves the cardiac performance.
- **Diuretics:** Frusemide, in a dose of 1–3 mg/kg orally and 0.5–1.5 mg/kg parenterally, relieves edema, pulmonary congestion and liver enlargement and thus helps in controlling heart failure.
- **Potassium:** Every patient of heart failure who is digitized and/or on diuretics should receive potassium supplements. Else, spironolactone, a potassium-sparing mild diuretic, serves as a valuable adjunct to frusemide in a dose of 1–4 mg/kg/day (oral) in two divided doses. Triamterene and amiloride may also be used.
- **Diet:** A low salt diet is ideal though there may, at times, be practical difficulties in giving it to infants. Increased energy needs from heart failure needs to be met.

Measures for Correction of the Underlying Cause

Correction of the underlying cause should be seriously considered. This is particularly important when heart failure is the result of or is precipitated/aggravated by anemia, nephrosis, overloading of circulation, severe chest infection, hypertension, fever, arrhythmias, pulmonary embolism, infective endocarditis, thyrotoxicosis, drug toxicity, etc. which can be taken care of without loss of much time. Surgically treatable causes like valvular lesions, obstructive lesions and shunts should be identified and adequately managed.

- **Refractory CCF:** Children with CCF that is refractory to the above-mentioned measures need:
 - Re-evaluation with a special search for unrecognized precipitating/underlying factor(s).
 - Therapy with a vasodilator nitroprusside, intravenous inotropic (dopamine) or beta blockers (propranolol) may be tried under strict hemodynamic monitoring (Box 27.3).
 - Ultrafiltration or dialysis in the presence of renal shutdown.
 - Cardiac transplantation with or without mechanical support may prove lifesaving following failure of all the measures (Box 27.4).

Box 27.3 Hemodynamic monitoring in heart failure

- Serum electrolytes
- Blood urea
- Serum creatinine
- Arterial pressure
- Urinary output
- Serum electrolytes.

Box 27.4 Stepwise-treatment of pediatric heart failure

- **Step 1:** Diuretics (frusemide) which improve the cardiac performance by reducing blood volume, peripheral vascular resistance and increasing the cardiac output.
- **Step 2:** Digoxin which improves cardiac contractility by its inotropic action, reduces cardiac work and decreases cardiac size.
- **Step 3:** Angiotensin-converting enzyme inhibitors (captopril, enalapril) with withdrawal of potassium-sparing diuretics or supplementary potassium is given with other diuretics.
- **Step 4:** Vasodilators, preferably nitrates, e.g. isosorbide dinitrate (oral) or sodium nitroprusside (IV).
- **Step 5:** Intermittent IV dopamine or dobutamine.
- **Step 6:** Beta blockers (propranolol) or steroids if active myocarditis present.
- **Step 7:** Heart transplantation.

Note: Steps 5–7 are usually needed in dilated cardiomyopathy.

CONGENITAL HEART DISEASE

Incidence

Incidence of CHD in the west is around 10 in 1,000 live births. As yet, figures on incidence in India are not available. About two-thirds of the patients suffering from CHD have surgically correctable lesions with gratifying prognosis, provided that the surgical intervention is done in the very first year of life. This, together with the increasing information regarding its significant incidence, highlights that it is worthwhile to make an early diagnosis of the exact cardiac anomaly.

Etiology

Maternal Infections

Maternal rubella and other teratogenic viral infections, like herpes simplex, during the first 3 months of pregnancy, seem to have a definite bearing.

Maternal Medication

Drugs such as thalidomide consumed during pregnancy, may cause CHD. So does idiopathic hypercalcemia.

Heredity

The role of heredity is not clearly understood. The incidence is higher among siblings. Also, siblings tend to suffer from the same disease. This author knows of a family with three siblings having ASD with bony defects, the so-called **Holt-Oram syndrome**. In another family, a brother and two sisters are suffering from VSD. In yet another case, a brother and a sister suffer from TOF; the brother—a known case of Down syndrome—recently developed right-sided hemiplegia following an episode of severe gastroenteritis.

Genetic Factors

Genetic factors may predispose to occurrence of CHD. For instance, gargoyism, Marfan syndrome. Holt-Oram syndromes, Ehlers-Danlos syndrome, etc.—all genetic disorders—are known to be accompanied by congenital heart lesions. Chromosomal defects, say Down syndrome, trisomy 13–15, trisomy 16–18, Turner syndrome, etc. are usually accompanied by CHD (Table 27.4).

Table 27.4: Cardiovascular anomalies in various syndromes/extracardiac lesions

Apert syndrome	VSD
Carpenter syndrome	PDA
CHARGE association (coloboma, heart disease, retardation, genital and ear anomalies)	VSD, ASD, PDA, TOF, ECD
CHILD (congenital hemidysplasia, ichthyosiform erythroderma, limb defects)	Miscellaneous
Congenital hypertrophic subaortic stenosis	VSD, PDA
Congenital rubella	PDA, peripheral pulmonic stenosis
Crouzon syndrome	PDA, COA
Cutis laxa	Pulmonary hypertension, pulmonary artery stenosis
Cornelia De Lange syndrome	VSD
DiGeorge sequence	Aortic arch anomalies, conotruncal anomalies
Down syndrome	VSD, ECD, ASD
Ellis-van Creveld syndrome	Single atrium, ADS
Familial dwarfism and nevi	Cardiomyopathy
Familial elfin facies, mental retardation, infantile hypercalcemia	Supravalvular aortic stenosis
FAVS (facio-auriculo-vertebral spectrum)	TOF, VSD
Fetal alcohol syndrome	ASD, VSD
Fetal hydantoin syndrome	VSD, ASD, COA, PDA
Fetal valproate syndrome	COA, hypoplastic left side of the heart, AS, PA, VSD
Holt–Oram syndrome	Familial ASD
Infants of diabetic mother anomalies	Hypertrophic cardiomyopathy, VSD, conotruncal anomalies
Jervell and Lange-Nielsen syndrome	Prolonged QT
Kartagener syndrome	Dextrocardia
Laurence–Moon–Biedl syndrome	Variable, including TOF
Marfan syndrome	Aortic or pulmonary artery dilatation, myocardial infarction
Noonan syndrome	PS, ASD, cardiomyopathy
Progeria	Accelerated atherosclerosis
Rubinstein–Taybi syndrome	PDA
Rubella syndrome	PDA, PS
Thrombocytopenia-absent radius (TAR)	ASD, TOF
Treacher Collins syndrome	VSD, PDA, ASD
Tuberous sclerosis	Myocardial rhabdomyoma
Ehler–Danlos syndrome	Arterial dilatation
Gargoylism	Multivalvular and coronary artery disease
Morquio–Ullrich	Aortic incompetence
Osteogenesis imperfecta	Aortic incompetence
Trisomy 13–15	VSD, PDA, ASD
Trisomy 16–18	VSD, PDA, PS
Turner syndrome	COA, PS, AS
VATER association (vertebral, anal, tracheoesophageal, radial and renal anomalies)	VSD, TOF, ECD

Abbreviations: ASD, atrial septal defect; COA, coarctation of the aorta; ECD, endocardial cushion defect; PA, pulmonary atresia; PDA, persistent ductus arteriosus; PS, pulmonary stenosis; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Environmental Factors

High altitude is said to exert considerable influence in causing CHD, especially in the susceptible hosts such as with hereditary predisposition. Both PDA and ASD are known to show higher incidences in population of high altitudes.

Associated Conditions

Congenital heart defect is frequently associated with other congenital defects. As for instance, cataracts, skeletal anomalies and deafness are observed with increasing

frequency in CHD. Down syndrome frequently has an associated cardiac anomaly such as atrioventricular canal, VSD or ASD, etc. Also, more and more new combinations are being reported.

Classification

Based on hemodynamics, CHD may be classified as follows:

■ **Cyanotic CHD:** Left-to-Right Shunt

- VSD
- ASD
- PDA

- 468 ■ Acyanotic CHD: Obstructive Lesions**
■ Right-sided: Pulmonary stenosis (valvular)

- **Left-sided**
 - Coarctation of aorta
 - Congenital aortic stenosis
 - Vascular rings
 - Anomalous origin of coronary arteries
 - Congenital mitral stenosis
 - Congenital mitral incompetence
 - Dextrocardia.

- **Cyanotic CHD: Right-to-Left Shunt**
 - Decreased pulmonary blood flow
 - TOF
 - Tricuspid atresia
 - Transposition of the great arteries (TGA) with:
 - VSD and PS
 - Double-outlet right ventricle with PS
 - Ebstein anomaly
- Increased pulmonary blood flow
 - Transposition of the great arteries
 - Persistent truncus arteriosus.

Diagnosis

Manifestations that raise high index of suspicion in early infancy include cyanosis, feeding problem, recurrent respiratory infections, failure to thrive (FTT) and features of specific chromosomal syndromes (trisomy 2, trisomy 13, trisomy 18, Turner syndrome, Noonan syndrome) and nonchromosomal syndromes (DiGeorge syndrome).

Characteristic Features of Three Groups of CHD

Characteristic features of three groups of CHD are listed in Table 27.5.

Additionally, Nada's criteria (as already described in this chapter) may be employed in infancy and childhood for presence of CHD. Among the imaging studies, though echocardiography is of paramount importance in neonates and infants, cardiac magnetic resonance imaging (MRI), computed tomography (CT) scan and diagnostic cardiac catheterization may be needed in older cases.

Spontaneous Closure/Corrections

- Small ASD and VSD usually close by 3 years of age.

- Patent ductus arteriosus, if it is to have a spontaneous closure, will do so in the first 2–4 weeks only.
- Muscular VSD has greater chances of closure than membranous VSD.
- Atrial septal defect involving fossa ovalis (not fossa secundum) may close spontaneously.

Treatment

Though catheter interventions for simple defects (ASD, muscular VSD, PDA) and balloon valvotomy for congenital pulmonary/aortic stenosis are now growing popular, corrective surgery should be considered the best choice for most of the defects.

Complications

These include:

- Infective endocarditis, FTT (common).
- Pulmonary arterial hypertension, polycythemia, hemiplegia, brain abscess, hypercyanotic (tet spells) (right-to-left shunt).
- Recurrent respiratory infections, heart failure, arrhythmias, aortic regurgitation (left-to-right shunt).

Prevention

- Prevention of rubella during pregnancy (through immunization in childhood or catch-up immunization in adolescence or later provided that there is no chance of conception within 2 months).
- Avoidance of consanguinity marriages and consumption of teratogenic agents during pregnancy.
- Medical termination of pregnancies with serious CHD detected by fetal echocardiography at 14–16 weeks of gestation.

Counseling

The chances of second child with CHD in parents who already have a child with such malformation are 2–5% only. However, in parents with two siblings suffering from such a problem, chances of third child also suffering from a cardiac defect are very high (20–25%).

In the first situation, parents need to be encouraged if they intend to have another child. In the second situation, such an advice would not be in order.

Table 27.5: Important features of three groups of congenital heart disease

Acyanotic: Left-to-right shunt	Acyanotic: Obstructive lesions	Cyanotic: Right-to-left shunt
<ul style="list-style-type: none"> ● Absence of cyanosis ● Frequent chest infections, including bronchopneumonia ● Tachypnea ● Proneness to congestive cardiac failure, often manifested as increased sweating ● Precordial bulge due to cardiomegaly ● Hyperkinetic precordium on palpation ● Tricuspid or mitral delayed diastolic murmur ● Chest X-ray—cardiomegaly, plethoric lung fields. 	<ul style="list-style-type: none"> ● Absence of cyanosis ● Absence of frequent chest infections ● Absence of precordial bulge ● Forcible or heaving cardiac impulse ● Thrill ● Ejection systolic murmur ● Absence of tricuspid and mitral delayed diastolic murmurs ● Delayed corresponding second sound. 	<ul style="list-style-type: none"> ● Cyanosis accompanied by polycythemia and clubbing ● Normal pulmonary arterial pressure ● Diminished pulmonary arterial pressure ● Here, pulmonary blood flow too is diminished due to pulmonary stenosis ● Increased pulmonary arterial pressure ● Increased pulmonary blood flow <ul style="list-style-type: none"> ■ Slight cyanosis ● Decreased pulmonary blood flow <ul style="list-style-type: none"> ■ Moderate to severe cyanosis ■ Irreversible pulmonary arterial hypertension ■ Poor prognosis.

VENTRICULAR SEPTAL DEFECT

Ventricular septal defect is the most common acyanotic CHD. It accounts for 25% of overall CHD. As high as 90% defects are in membranous portion of the interventricular septum; only 10% defects are in muscular septum.

Classification

Various classifications of VSD are given in Box 27.5.

Hemodynamics/Pathophysiology

The size of the left-to-right shunt depends on two determinants, namely the size of the VSD (largely) and the pulmonary vascular resistance (PVR) in relation to systemic vascular resistance. In case of a **restrictive VSD** (under 0.5 cm), higher pressure in the left ventricle is able to cause only a limited left-to-right shunt.

In case of a **nonrestrictive VSD** (large, usually over 1 cm), pulmonary vascular resistance at birth is higher than normal. The magnitude of the shunt from left-to-right is, therefore, limited. However, with the reduction in the resistance in the next few weeks, the shunt magnitude

increases. When the shunt magnitude becomes quite large, **469** VSD becomes symptomatic.

With passage of time, pulmonary vascular obstructive disease begins to develop. As soon as ratio of pulmonary to systemic vascular resistance approaches 1:1, the shunt becomes bidirectional. At this point, the child becomes cyanotic with disappearance of CCF signs. This state is called **Eisenmenger complex or syndrome**.

The enlargement of the chambers depends on the shunts which further depend on the ratio of the pulmonary to systemic blood flow. When the ratio is under 1.75:1, the shunt is small, appreciable enlargement of the chambers does not occur and pulmonary vascular bed is by and large normal.

When, on the contrary, the ratio is above 2.5:1, the shunt is large, and left atrial and ventricular volume overload and right ventricular and pulmonary arterial hypertension occur. The large volume of pulmonary blood flow causes enlargement of the pulmonary artery trunk, left atrium and left ventricle.

Clinical Features

If septal defect is small, there may be no symptoms at all. The disease is detected incidentally during a routine clinical examination. Large defect causes recurrent chest infections, CCF, FTT, exertional dyspnea, etc. In symptomatic patients, heart is moderately or greatly enlarged (usually biventricular).

The characteristic murmur is a loud pansystolic, heard maximal down the left sternal border—best in the 3rd intercostal space (second aortic area), but also in 4th and 5th intercostal space. It is usually accompanied by a thrill. A functional diastolic murmur, due to large blood flow across the mitral valve, may be present over apex.

In the presence of pulmonary hypertension, pulmonary second sound (P2), which is split, becomes accentuated. In such patients, a pulmonary diastolic murmur may also be found. In older children, the additional findings may be in the form of wide pulse pressure and an early diastolic murmur at the base. These findings suggest development of aortic regurgitation as a complication of VSD (usually subpulmonic).

Diagnosis

- **X-ray chest** is usually normal. Minimal cardiomegaly and slight increase in pulmonary vascularity may be noticed in all defects. In large VSD, it shows a large left-to-right shunt with enlarged heart (both ventricles and left atrium), enlarged pulmonary artery and plethoric lung fields (overvascularity) with or without hilar dance (Fig. 27.3).
- **Electrocardiography** in small defects is usually normal but may show LVH. In large defects, ECG shows biventricular hypertrophy with notched or peaked P waves.
- The **two-dimensional echocardiogram** reveals volume overload of the left ventricle and left atrium, and the position and size of the septal defect (Fig. 27.4).

Box 27.5 Classifications of ventricular septal defect

- **Anatomic classification**
 - Perimembranous (subaortic, infracristal)—accounts for 75% of all VSDs
 - Muscular (anterior, mid-muscular or apical)—accounts for 5–20% of all VSDs
 - Inlet (inflow, canal VSD)—accounts for 5–8% of all VSDs
 - Outlet (subpulmonic).
- **Geodynamic classification**
 - **Group 1:** Small VSD, normal PVR, small left-to-right shunt—Asymptomatic
 - **Group 2:** Moderate VSD, variable PVR, significant left-to-right shunt—Some FTT and cardiomegaly
 - **Group 3:** Large VSD, moderately high PVR, significant left-to-right shunt—Symptomatic with CCF
 - **Group 4:** Large VSD, very high PVR, small or no left-to-right shunt, or right-to-left shunt—Symptomatic with cyanosis and PAH.
- **ECHO-based classification**
 - **Large:** Defect—diameter of aorta
 - **Moderate:** One-third to two-thirds of diameter of aorta
 - **Small:** Less than one-third of diameter of aorta
 - **Pinhole:** Less than 2 mm (detectable by color Doppler only).
- **Classification-based on number of septal defects**
 - **Single**
 - **Multiple:** Swiss-cheese type.
- **Classification-based on site of septal defect**
 - **Supracristal:** Above crista supraventricularis (infrequent)
 - **Infracristal:** Below crista supraventricularis (most common)
 - ◆ **Membranous**
 - ◆ **Muscular:** Inlet, trabecular, infundibular.
- **Classification-based on flow of blood**
 - **Restrictive:** Septal defect <0.5 cm
 - **Nonrestrictive:** Septal defect >1 cm.

Abbreviations: CCF, congestive cardiac failure; FTT, failure to thrive; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; VSD, ventricular septal defect.

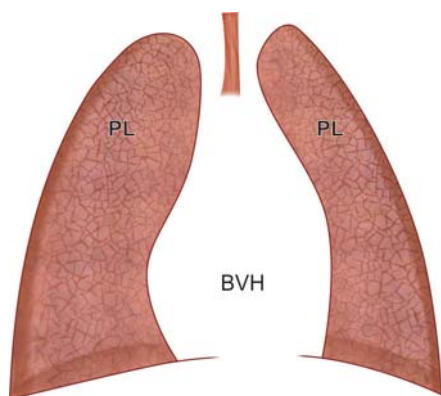


Fig. 27.3: Classical chest X-ray appearance of a large VSD.
Abbreviations: PL, plethoric lung; BVH, biventricular hypertrophy.

- **Cardiac catheterization** and **selective angiocardiography** are of much help in locating the site of the shunt.

Natural History/Course

An overwhelming proportion of small VSDs (60–90%) undergo spontaneous closure by 3 years. The moderate VSDs close in only 10% cases whereas large VSDs only infrequently close spontaneously. Nevertheless, reduction in size may occur often in small and moderate VSDs and occasionally in large VSDs. Of the two types, it is the muscular VSD that stands greater chance of spontaneous closure.

Complications

- Failure to thrive/growth failure
- Recurrent pneumonia
- **Infective endocarditis:** VSD is the most common CHD to develop infective endocarditis. Supracristal VSD carries the maximum risk
- Repeated episodes of heart failure
- Pulmonary arterial hypertension and its complications (Eisenmenger syndrome)
- Pulmonary stenosis (Gasul's VSD)
- Aortic regurgitation (rare; invariably in supracristal VSD).

Treatment

General measures include attention to good nutrition with treatment of iron deficiency anemia and other nutritional deficiency states. Heart failure and recurrent chest infection are treated on usual lines. Antibiotic prophylaxis for endocarditis is indicated. Box 27.6 lists indications of corrective surgery, using a patch in VSD. Surgery should not be done in cases of:

- Small VSD
- Severe pulmonary arterial hypertension
- Significant reversal of shunt, i.e. right-to-left shunt (Eisenmenger syndrome).

Successful corrective surgery can be performed even in infants, including those with FTT. The age of the patient

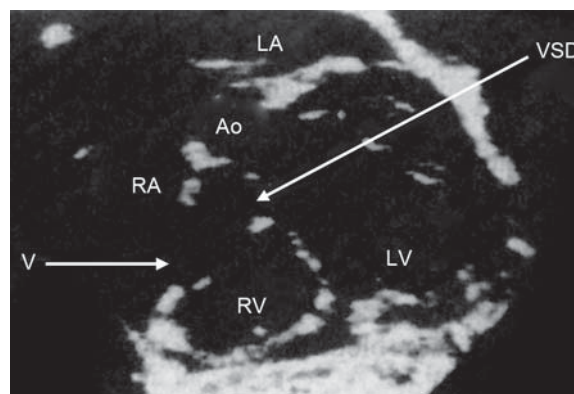


Fig. 27.4: Echocardiography (subcostal four-chamber view) of a ventricular septal defect.

Abbreviations: LA, left atrium; AO, aorta; LV, left ventricle; RA, right atrium; RV, right ventricle; VSD, ventricular septal defect.

Box 27.6 Indications of surgery in VSD

- Symptomatic VSD where medical therapy has failed to control symptoms, regardless of age
- VSD with occurrence of heart failure in infancy
- Large VSD with PAH, pulmonary hypertension or aortic regurgitation
- Supracristal VSD at any age
- VSD subject over 2 years of age with pulmonary flow (Qp): systemic flow (Qs) ratio >2:1.

Abbreviations: PAH, pulmonary arterial hypertension; VSD, ventricular septal defect.

and poor growth are, therefore, not the deciding factor for surgery. Complications of corrective surgery, though rare, include:

- Complete heart block
- Bifascicular heart block (with membranous VSD)
- Residual/reopened VSD.

Long-term prognosis following corrective surgery is excellent. In muscular VSD (occurring in just 10% cases) in older children, catheter (device) closure may be done. This technique carries considerable risk of complete heart block in membranous VSD.

ATRIAL SEPTAL DEFECT*

Patency of foramen ovale has no clinical significance. Ostium secundum defect (high in atrial septum) may be as large as 2 cm. It occurs three times more in females than in males.

Rarely, it is associated with mitral stenosis (Lutembacher syndrome). In Holt-Oram syndrome, ASD is associated with skeletal deformities of the upper limb and hypoplasia of the clavicle (Fig. 27.5). In Ellis-van Creveld syndrome, it exists in association with chondrodystrophic dwarfism and polydactyly, conical teeth, multiple frenulum and nail dysplasia.

Hemodynamics/Pathophysiology

The magnitude of the left-to-right shunt depends on size of the ASD, relative compliance of the two ventricles, and

* Atrial septal defect was the first congenital heart disease recognized as far back as in 1531 by Leonardo da Vinci.

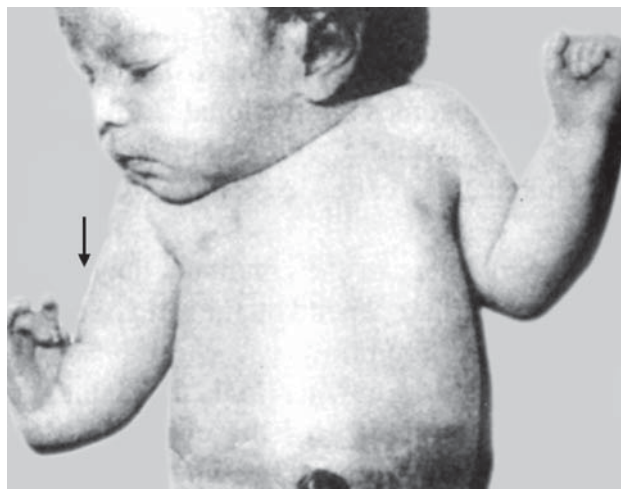


Fig. 27.5: Holt-Oram syndrome. Note phocomelia with hypoplasia of the thumb and clavicle on right side in a child with atrial septal defect (large ostium secundum defect).

relative vascular resistance in the pulmonary and systemic circulations.

In a large ASD, pulmonary blood flow becomes 2–3 times the systemic flow. Yet, symptoms are absent or minimal in infants because the greater thickness and less resilience of muscular wall of the right ventricle limits the shunt. As the infant grows, the right ventricular wall becomes thin and more resilient, causing elevation in the shunt. Enlargement of the right atrium and ventricle and dilation of the pulmonary artery result from passage of large blood flow through the right heart. Nevertheless, pulmonary arterial pressure remains normal, pulmonary vascular resistance low and the left ventricle and aorta normal in size. In adulthood, when pulmonary vascular resistance begins to increase, cyanosis may occasionally develop.

Clinical Features

Atrial septal defect remains asymptomatic in most of the infants and young children. Older children may have recurrent chest infection, breathlessness and bulging of the chest due to enlargement of right ventricle. Another important feature is growth failure, which may be the only manifestation in some children.

The typical murmur is ejection systolic, soft, and best heard over upper left sternal border (usually the second intercostal space). It is preceded by a loud first sound and may be radiated to the apex and back. Intensity of the murmur reflects the size of the shunt. Louder murmur points to a large shunt. P2 is widely split and fixed.

Diagnosis

- **Chest X-ray** shows right atrial and ventricular enlargement, increased pulmonary vascularity, enlarged pulmonary artery and rather small left ventricle and aorta (Fig. 27.6).
- **Electrocardiography** reveals RVH and right axis deviation. **Echocardiography** shows evidence typical of right ventricle overload, say:



Fig. 27.6: Classical X-ray appearance of an atrial septal defect. Note enlarged right atrial border and cardiomegaly.

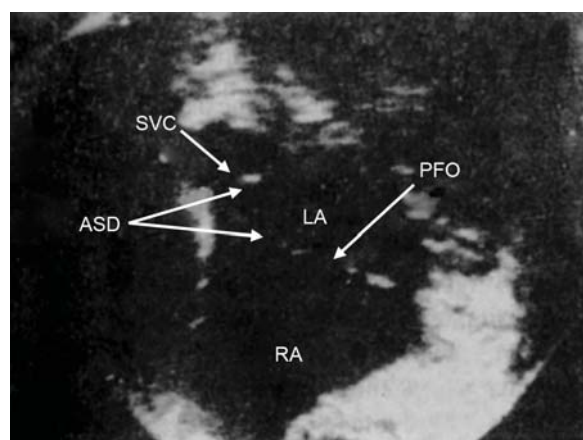


Fig. 27.7: Echocardiography (two-dimensional) of a sinus venosus atrial septal defect.

Abbreviations: SVC, superior vena cava; ASD, atrial septal defect; PFO, patent foramen ovale.

- Increased ventricular end-diastolic dimension.
- Reversal of ventricular septal motion.
- Localization of the exact size and position of atrial defect by real-time two-dimensional scans from apical position (Fig. 27.7).
- **Cardiac catheterization** shows oxygen content of blood from right atrium to be far more than that from superior vena cava.

Complications

These are infrequent, especially in infants:

- Heart failure seldom occurs in infancy
- Infective endocarditis is infrequent
- Pulmonary hypertension
- Eisenmenger complex
- Paradoxical embolism—here emboli from the extremities cross the ASD and enter the systemic circulation without getting opportunity to be filtered by the lungs as in a normal case.

472 Treatment

- Heart failure and arrhythmias should be managed medically.
- Antibiotic prophylaxis during dental procedures is necessary.
- In view of risk of complications, closure of defects, if needed, should be done before school entry.
- Small defects (<8 mm) are likely to undergo spontaneous closure and are best observed and followed up.
- Fossa ovalis defects usually respond to occlusive devices placed percutaneously through catheter. A proportion of them need surgical closure.
- The closure of defect by open heart surgery gives gratifying results. It is best done in childhood.

PATENT DUCTUS ARTERIOSUS

Patent ductus arteriosus, persistence of a communication between aorta and pulmonary artery, is unique in two ways. Firstly, it occurs most often as an isolated defect which is unlike most other congenital cardiac anomalies. Secondly, it occurs twice as frequently in girls as in boys.

Hemodynamics/Pathophysiology

The magnitude of the right-to-left shunt depends on the size of the ductus and the ratio of the pulmonary to systemic vascular resistance.

Since pressure gradient in aorta is dominant, blood flow is from aorta to pulmonary artery. In advanced cases, almost half or more of left ventricular output may be shunted through the ductus. In extreme degree of disease, pulmonary hypertension may develop. If left untreated, such a patient may develop pulmonary vascular disease.

Run off of blood into pulmonary artery during systole accounts for the high pulse pressure.

Clinical Features

Patent ductus arteriosus may become manifest with heart failure in second or third month of life. Symptomatic cases have growth retardation, recurrent respiratory infections, exertional dyspnea (effort intolerance), palpitations, and heart failure. Occasionally, precordial pain and hoarseness (due to recurrent laryngeal nerve involvement) may be present. Pulse pressure is wide because of leak of systemic blood from aorta to pulmonary artery. As a result, **water-hammer pulse** and prominent arterial **Corrigan (carotid) pulsations** in the neck may be present. **Differential cyanosis**, in which left arm and both feet are involved, may be observed.

The **classical PDA murmur** develops some weeks or months after birth only. It begins immediately after the first heart sound and reaches its peak at the end of systole. It continues in a reduced intensity during most of diastolic phase (though audible during a part of diastolic phase), gradually disappearing in the later part. This is what has been described as **machinery murmur**. It is harsh and best heard at the second left intercostal space away from the left sternal border (Gibson's area) and transmitted to area below the left clavicle, and, at times, lower down, i.e. left sternal border. It is usually accompanied by a thrill.

Box 27.7 Differential diagnosis of continuous murmur

- VSD with aortic regurgitation
- Coronary arteriovenous fistula
- Systemic arteriovenous fistula over the chest
- Pulmonary arteriovenous fistula
- Venous hum
- Ruptured sinus of Valsalva fistulae into the right side
- Bronchial collateral murmurs
- Peripheral pulmonic stenosis
- Total anomalous pulmonary venous connection
- A small ASD + mitral stenosis (Lutembacher syndrome).

Abbreviations: ASD, atrial septal defect; VSD, ventricular septal defect.

In case of a large shunt, a third heart sound followed by a delayed diastolic murmur may be audible. Box 27.7 lists the differential diagnosis of a continuous murmur. There may be **paradoxical splitting of P2**.

Complications

- Heart failure
- Infective endocarditis
- Pulmonary arterial hypertension
- Rarely, aneurysmal dilatation of pulmonary artery and/or ductus, calcification of ductus, thromboembolism, Eisenmenger syndrome and rheumatic heart disease.

Diagnosis

- **Radiology** reveals biventricular enlargement, prominent aortic knob and pulmonary artery and plethoric lungs with hilar dance (Fig. 27.8).
- **Electrocardiography** is usually normal, but may show ventricular hypertrophy. Deep Q waves may be seen in left ventricular leads.
- **Echocardiogram** is essentially normal in a small ductus. In case of a large ductus, there is an increase in left atrial and ventricular dimensions and decrease in isovolumetric contraction time (Fig. 27.9).

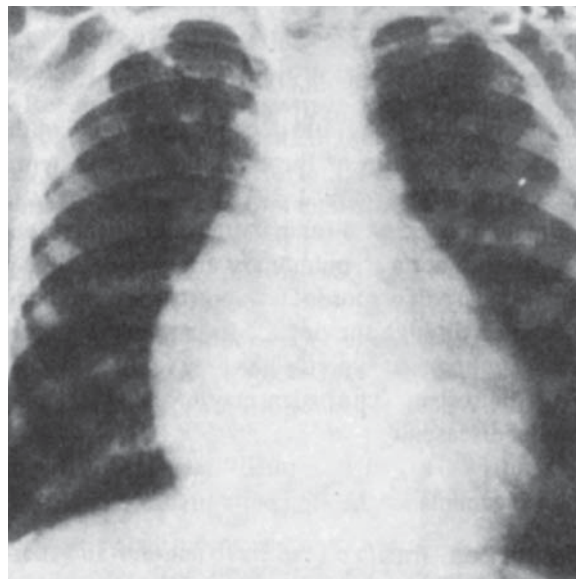


Fig. 27.8: X-ray chest showing cardiomegaly, prominent aortic arch and pulmonary artery in patient with patent ductus arteriosus.

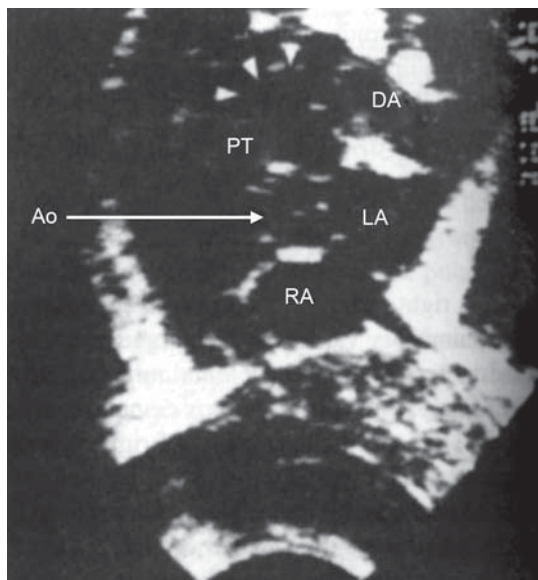


Fig. 27.9: Echocardiography (two-dimensional) in patent ductus arteriosus.

- **Cardiac catheterization** shows presence of oxygenated blood in the pulmonary artery and normal or raised pressure in right ventricle and pulmonary artery.

Treatment

- For medical closure of PDA, encouraging results are obtained with the use of antiprostaglandin agent indomethacin that inhibits prostaglandin E1 synthesis in infants with PDA in the first 2 weeks of birth. At 2–7 days' age, dose is 0.2 mg/kg/dose given in 3 oral or IV doses at 12–24 hour intervals. Alternatively, ibuprofen, mefenamic acid or aspirin may be used.
- Surgical intervention (ligation or division) is indicated in neonates who fail to respond to medical treatment.
- Alternatively, catheter-based treatment (occlusive devices), which is much more expensive than surgery, may be offered.
- Medical management consists in tackling CCF and prevention and treatment of infective endarteritis.
- Natural closure of PDA may occur in a small proportion of cases. If this is to happen, it will do so before the child has crossed his first birthday.
- Asymptomatic PDA should be treated by ligation or division of the ductus or employing occlusive devices, preferably between 3 years and 10 years of age.

TETRALOGY OF FALLOT*

It is the most common cyanotic CHD. Its four essential components (tetrad) are—(1) Pulmonary stenosis (usually infundibular), (2) Ventricular septal defect, (3) Right ventricular hypertrophy and (4) Dextroposition/over-riding of the aorta.

Hemodynamics/Pathophysiology

Pulmonary stenosis and VSDs are the most vital abnormalities in TOF. The VSD is generally of the perimembranous

variety with extension into the outlet septum of the right ventricle, and is large and nonrestrictive, allowing equalization of pressure between the right and the left ventricle. **473**

Pulmonary stenosis affects both the infundibulum and the pulmonary valve and artery. Infundibular stenosis is in part because of anterior deviation of the infundibular portion of the ventricular septum. Pulmonary stenosis is almost always present, though it is seldom the only site of obstruction. The spectrum of severity of disease in TOF is determined by the degree of obstruction of the right ventricle outflow tract.

When the right ventricle contracts, it meets much resistance at the pulmonary stenosis. The right-sided blood is, therefore, shunted through the ventricular defect into the left ventricle and then on to aorta. The net result is persistent arterial unsaturation, polycythemia, cyanosis and poor pulmonary vascularity.

Occasionally, the degree of obstruction is small and the right-to-left shunt is minimal or absent. This mild form is termed **pink** or **acyanotic TOF**.

Clinical Features

Manifestations of Fallot tetralogy usually become evident after the closure of the ductus arteriosus begins. Cyanosis of lips and nail bed (blue baby) and dyspnea are the earliest presenting features. The intensity of cyanosis is directly proportional to the severity of pulmonary stenosis. As the child grows, he feels comfortable while lying down or in **squatting position** only. **Anoxic, hypoxic** or **blue (hypercyanotic) spells** may occur due to cerebral anoxia. Such spells consist of dyspnea and cyanosis with or without unconsciousness. By the age of 2 years, the child usually develops some clubbing (Fig. 27.10).

Heart failure is unusual in infants and children suffering from TOF, perhaps never as a result of classical



Fig. 27.10: Gross clubbing in a girl with tetralogy of Fallot.

* Tetralogy of Fallot is named after the French physician, Etienne Fallot (1850–1911), who first described it in 1888.

474 TOF per se. Reason—the VSD is able to decompress the right ventricle.

- **Infants with mild outflow obstruction** (pink or acyanotic TOF) usually develop cyanosis in the later part of first year (often 6–12 months of age). They may initially present with heart failure due to a ventricular level left-to-right shunt.
- **Infants with severe outflow obstruction** develop cyanosis immediately in the neonatal period, usually in first few hours or days of life when the ductus arteriosus begins to close.

The typical murmur is loud short systolic, at left sternal border in third space. It is generally not accompanied by a thrill. This murmur is soft rather than harsh in very severe degree of the disease. P2 is usually single. There is an inverse relationship of the intensity of the systolic murmur to the severity of pulmonary stenosis. Shorter the murmur, more is the severity of pulmonary stenosis.

Diagnosis

- **Blood studies** show polycythemia and high hematocrit (packed cell volume).
- **Chest X-ray** (Figs 27.11 and 27.12) reveals **oligemic lung fields** (poorly vascularized lungs), a small boot-shaped heart (coeur en sabot) with the tip of the boot turned up above the diaphragm (because of RVH), and concavity of the pulmonary artery segment (small pulmonary conus). One in every 4 or 5 cases of TOF has right aortic arch.
- **Electrocardiography** shows right axis deviation, RVH with tall and beaked P waves.
- The **two-dimensional echocardiography** shows the anterior-superior displacement of the outflow ventricular septum, causing stenosis of the subpulmonic right ventricular outflow (Fig. 27.13).
- Cardiac catheterization and selective angiocardiography are of great value to elucidate anatomic

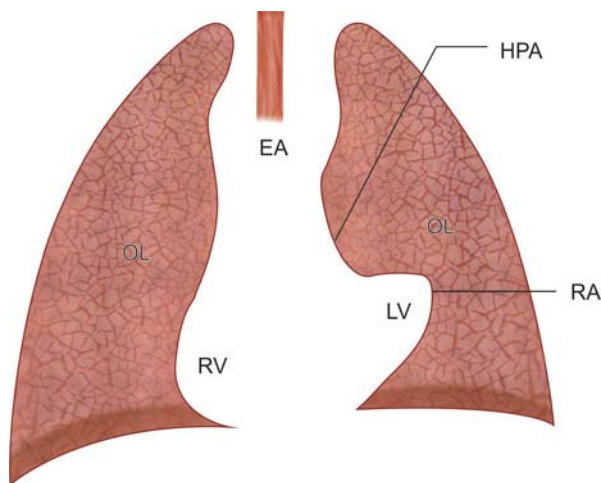


Fig. 27.11: Classical X-ray appearance of tetralogy of Fallot. Note the boot-shaped heart.

Abbreviations: EA, enlarged aorta; RA, raised apex; RV, right ventricle; OL, oligemic lung; HPA, hypoplastic pulmonary artery (pulmonary concavity or bay); LV, left ventricle.

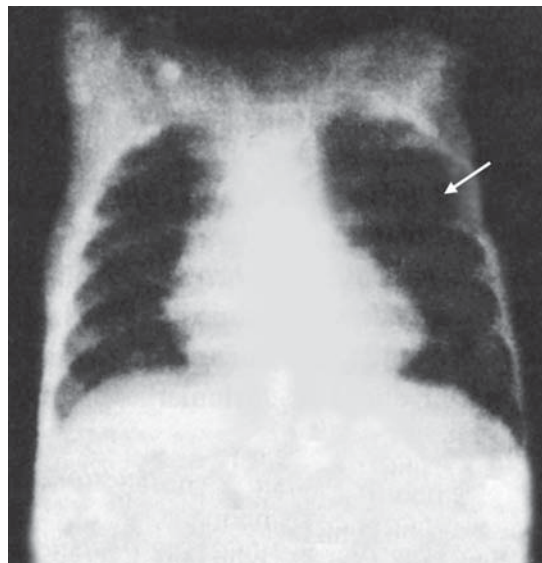


Fig. 27.12: Chest X-ray in tetralogy of Fallot. Note the boot-shaped heart and oligemic lung fields.

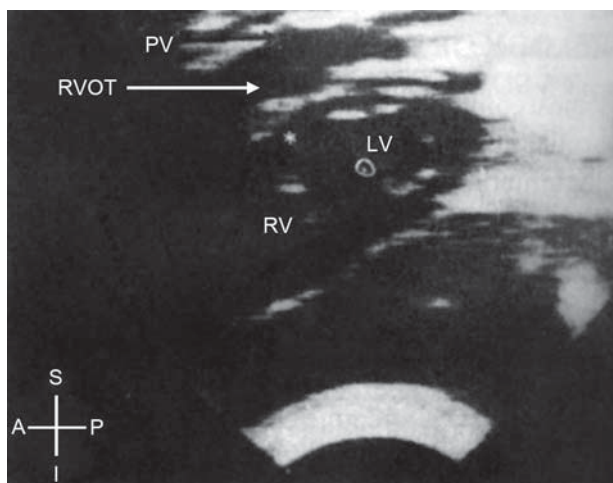


Fig. 27.13: Echocardiography (two-dimensional) in tetralogy of Fallot. **Abbreviation:** RVOT, right ventricular outflow tract.

anomalies in tract and associated anterior VSD in doubtful cases. **Cardiac catheterization** shows remarkable fall in systolic pressure in the right ventricle as the catheter enters the pulmonary artery.

- **Ventriculography** shows the anatomy of TOF at its best.
- **Aortography/coronary arteriography** outlines the course of the coronary arteries.

Complications

- Hemiplegia from cerebral thrombosis (especially in the presence of diarrheal dehydration and dyselectrolytemia), anoxic infarction in the course of hypercyanotic spells, paradoxical embolism, brain abscess, etc.
- Brain abscess—it usually manifests with irritability, headache, seizures, vomiting, fever and hemiplegia.
- Bleeding diathesis
- Infective endocarditis
- Heart failure, though not a feature of TOF as such, may occasionally occur in TOF children with gross

iron-deficiency anemia, or in young infants with pink or acyanotic TOF. Additionally, it may occur in TOF with infective endocarditis, hypertension (systemic), aortic-pulmonary valve regurgitation and myocarditis.

Associated Cardiovascular Anomalies

These include PDA, ASD, right aortic arch, anomalies of pulmonary arteries and aortic arch, persistence of a left superior vena cava, multiple VSDs, atrioventricular septal defects (often in Down syndrome), congenital absence of the pulmonary valve, marked aneurysmal dilatation of the main and branch pulmonary arteries, and absence of a branch pulmonary artery.

Treatment

- **General measures** include correction of iron-deficiency anemia and dehydration and an appropriate antibiotic for bacterial infection.
- **Management of hypercyanotic spells:** Mild sedative like promethazine reduces the frequency of spells, provided it is given regularly. Oral propranolol therapy is of value in prevention. The optimal dose is 0.5–1.0 mg/kg (maximum 1.5 mg/kg) orally every 6 hours. Iron-deficiency anemia, if coexisting, should also be treated. Nevertheless, the best approach is to refer the child for surgical treatment as soon as he starts having spells. Selective treatment of acute hypercyanotic spell is outlined in Box 27.8.

Neonates with severe TOF are likely to deteriorate rapidly since the ductus arteriosus does not remain sufficiently patent to allow enough pulmonary blood flow. Pending surgery, they benefit considerably from prostaglandin E1 (intravenously) which causes dilatation of the ductus and allows adequate pulmonary blood flow. It should be administered immediately on making diagnosis of cyanotic CHD in a dose of 0.05–0.20 µg/kg/minute and continued through cardiac catheterization and surgery to briefly within postoperative period.

Surgery

Surgery is possible if pulmonary artery is of adequate size. With surgery, the patient lives a normal life. Without it, death usually occurs within 20 years.

Box 27.8 Selective treatment of hypercyanotic spells

- Comfort the child and place in knee-chest position
- Administer humidified O₂ by face mask
- Give morphine, 0.1–0.2 mg/kg IV
- Begin IV fluid replacement and volume expansion (if child is anemic, administer blood)
- Treat acidosis with sodium bicarbonates
- Administer propranolol, 0.1–0.2 mg/kg IV
- Increase systemic vascular resistance by IV administration of vasopressors like methoxamine or phenylephrine. Titrate dose to increase systemic systolic blood pressure by 20%. In no case, this step should be allowed to postpone surgical intervention
- Operate to repair defect or to establish systemic-to-pulmonary artery anastomosis.

Palliative Surgery

- **Modified Blalock-Taussig shunt:** It consists in anastomosing the subclavian and the pulmonary arteries. This is the most popular systemic-to-pulmonary artery shunt today. It can be performed successfully even in a preterm neonate.
- Balloon dilation of pulmonary valve:
 - Stenting of patent arterial duct in case it is present.
 - Potts' operation—here, a side-to-side anastomosis of pulmonary artery with aorta is created.
- **Waterson's operation:** It consists in constructing a shunt between the ascending aorta and the right pulmonary artery.

Total Correction (Definitive Surgery)

Direct-vision open heart surgery for repair of VSD and pulmonary stenosis later in childhood is the procedure of choice under ideal circumstances. Total correction carries a mortality of 15%. Those who survive operation show complete disappearance of cyanosis and clubbing, and improvement in growth and development. Nevertheless, risk of heart failure and **sudden death** due to arrhythmias as also exercise disability remains high. Infrequently, a permanent complete heart block may occur following surgery. It is an indication for placement of a permanently implanted pacemaker.

FALLOT'S PHYSIOLOGY

This term is applied to the following five situations in which two of the major features of TOF, i.e. a large VSD and pulmonary stenosis together, occur in association with another major congenital cardiac defect:

- Transposition of the great arteries with VSD and pulmonary stenosis.
- Double-outlet right ventricle with pulmonary stenosis and a large subaortic VSD.
- Tricuspid atresia with decreased blood flow.
- Single ventricle with pulmonary stenosis.
- Corrected TGA with VSD and pulmonary stenosis.

Clinically, it is almost impossible to differentiate them from the TOF since the symptoms and signs are by and large identical. ECG is of limited value (except in tricuspid atresia with decreased blood flow) but echocardiography has a vital role in the differential diagnosis (Table 27.6). Nevertheless, like TOF, all these conditions are surgically correctable.

TRICUSPID ATRESIA

The term denotes congenital absence of tricuspid valve, resulting in absence of any outlet from the right atrium to right ventricle. The entire systemic venous return, therefore, enters the left heart by means of the foramen ovale or an ASD.

Hemodynamics/Pathophysiology

Consequent to the entry of systemic blood through the foramen ovale or ASD into the left atrium from right atrium, there occurs a complete mixing of the systemic venous and pulmonary venous bloods. From the left atrium, the

Table 27.6: ECG and echocardiogram in Fallot's tetralogy and Fallot's physiology

Conditions	ECG changes	Echocardiographic changes
Tetralogy of Fallot	Right axis deviation, right ventricular hypertrophy, tall and beaked (occasionally bifid) and P wave	<i>Diagnostic:</i> Extent of aortic over-riding of the septum, right ventricular outflow tract obstruction, size of proximal branch pulmonary arteries, side of aortic arch, status of PDA
Double-outlet right ventricle with pulmonary stenosis and a large VSD	Right axis deviation, right ventricular hypertrophy	Both great vessels arising from right ventricle, mitral-aortic valve discontinuity
Tricuspid atresia with decreased blood flow	<i>Diagnostic:</i> Left axis deviation and LVH, QRS axis about -45° , P wave showing PAH and LAH	Only one ventricle and one A-V valve
Single ventricle with pulmonary stenosis	Left axis deviation with RVH or right axis deviation with LVH, monophasic or equiphase QRS complex in all precordial leads	Absence or near absence of ventricular septum, whether single ventricle has right, left, or mixed morphology, rudimentary outflow chamber under a great vessel, bulboventricular foramen
Corrected transposition of the great arteries with ventricular septal defect and pulmonary stenosis	Right axis deviation, RVH, LVH, occasionally tall spiked P waves.	Inversion of ventricles

Abbreviations: LAH, left anterior hypertrophy; LVH, left ventricular hypertrophy; PDA, patent ductus arteriosus; RVH, right ventricular hypertrophy; PAH, pulmonary arterial hypertension; VSD, ventricular septal defect; ECG, electrocardiogram.

mixed blood passes to the left ventricle. From the left ventricle, it crosses over to the right ventricle through a VSD. The size of this VSD and the presence and severity of pulmonary stenosis (which decreases the pulmonary blood flow) determine the degree of cyanosis with which most subjects present in early months.

Around 30% cases of tricuspid atresia may have associated TGA. The pulmonary blood flow in these cases is usually increased. Hence, they develop CCF early.

Clinical Features

In 90% cases, pulmonary blood flow is decreased. They have early onset of cyanosis and other features of TOF with the following exceptions:

- Left ventricular apical impulse instead of right ventricular impulse.
- Holosystolic murmur along the left sternal border with a single second heart sound.
- Prominent *a* waves in jugular venous pulse.
- Hepatomegaly with *a* waves (presystolic pulsations).

Diagnosis

- In a large majority of the cases, chest X-ray shows pulmonary undercirculation (oligemia). Only in a small proportion (with TGA), overcirculation (plethora) is seen.
- **Electrocardiography** is characteristic with left axis deviation and LVH with a mean QRS axis about -45° . P waves are consistent with both RVH and LVH.
- **The two-dimensional echocardiogram** shows replacement of the tricuspid valve by a fibromuscular membrane, a small right ventricle, VSD and a large left ventricle (Fig. 27.14).
- **Cardiac catheterization** shows normal or slightly increased right atrial pressure with a prominent *a* wave.

Treatment

Medical treatment is on more or less the same lines as for TOF. An infusion of prostaglandin E1 is strongly

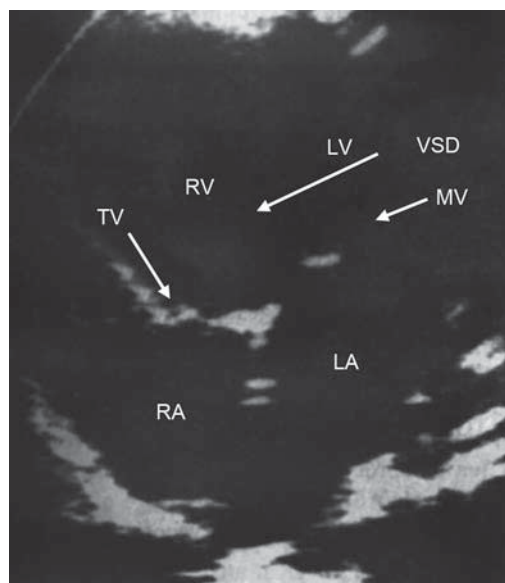


Fig. 27.14: Echocardiography (two-dimensional apical four-chamber view) demonstrating VSD and tricuspid atresia along with transposition of the great arteries.

Abbreviations: LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve; VSD, ventricular septal defect.

recommended in severely cyanotic neonates while waiting for the surgical intervention to improve pulmonary blood flow. Adequacy of the pulmonary flow determines the type of surgical intervention. For most of the cases (decreased pulmonary flow), an aortopulmonary shunt procedure is required. The preferred choice is **Blalock-Taussig shunt**. For the patients with increased pulmonary flow (TGA), pulmonary arterial banding is indicated.

Bidirectional Glenn shunt involves creation of an anastomosis between the superior vena cava and the pulmonary arteries. It is usually performed at the age of 4–12 months when the patient has outgrown the benefits of previous shunt.

Modified Fontan operation is the preferred approach at the ages of 1½–3 years. It involves caval-pulmonary isolation in which the inferior vena cava is anastomosed to the pulmonary arteries via a baffle that runs along the lateral wall of the right atrium.

The ASD/foramen ovale is also closed. Following this operation, the volume load is removed in toto from the left ventricle. The right-to-left shunt too is abolished. This operation may have postoperative complications in the form of pleural effusion in 5% cases, and late problems such as superior or inferior vena caval syndrome, vena caval/pulmonary artery thromboembolism, protein-losing enteropathy, supraventricular arrhythmias, and left ventricular dysfunction after or during adolescence.

EBSTEIN ANOMALY

This rare cyanotic CHD is characterized by diminished pulmonary blood flow as a result of downward displacement of the abnormal tricuspid valve with malformed and fused leaflets into the right ventricle. The contraction of right ventricle becomes abnormal and, above the attachment of the leaflet, it gets thinned down (atrialized right ventricle).

Hemodynamics/Pathophysiology

The abnormal tricuspid valve (all cusps except anterior) divides the right ventricle into two parts, an atrialized part that is continuous with the right atrium and a normal portion consisting of myocardial tissue. As a result, right atrium becomes huge. The tricuspid valve turns regurgitant. Also, there is variable magnitude of obstruction of the right ventricular outflow tract. The effective output from the right side of the heart is reduced and right ventricular function compromised. A right-to-left shunt through foramen ovale/ASD may allow passage of right atrial blood to the left atrium, causing cyanosis. The severity of cyanosis varies with the extent of displacement of the tricuspid valve.

Clinical Features

Manifestations depend on magnitude of displacement of the tricuspid valve and right ventricular outflow tract obstruction. These include cyanosis, effort intolerance, fatigue, attacks of paroxysmal tachycardia, extrasystoles or other cardiac dysrhythmias.

The precordium is quiet but a holosystolic murmur (with a thrill) is heard over most of the anterior left side of the chest. There is also a superficial scratchy diastolic murmur at the left sternal border. This murmur resembles a pericardial friction rub. The presentation of Ebstein anomaly in neonates is frequently with severe cyanosis, massive cardiomegaly with heart failure and long systolic murmurs.

Diagnosis

- **Electrocardiography** shows classical changes in the form of a right bundle branch block, P pulmonale, P mitrale and a normal or prolonged P-R interval. Wolf-Parkinson-White (WPW) pattern may sometimes be observed.

- **X-ray chest** may show normal to massive box-like cardiomegaly from enlargement of right atrium and right ventricle, prominent main pulmonary segment, small aortic knuckle and diminished lung vascularity (oligemic lungs).
- Two-dimensional **echocardiography** revealing the displaced tricuspid valve, a dilated right atrium, a right ventricular outflow tract obstruction, tricuspid regurgitation, and, in severe cases, immobile pulmonary valve, is diagnostic.
- **Intracardiac electrocardiogram** showing catheter is in the ventricle and the pressure recording showing right atrial type of pressure.
- **Cardiac catheterization** and **selective angiocardio-graphy** establish the existence of a large right atrium, an abnormal tricuspid valve and a right-to-left shunt.

Treatment

The surgical intervention in a neonate with severe disease aims at creating a functional tricuspid atresia by a patch closure to the valve, atrial septectomy and placement of an aortopulmonary shunt (**Starnes procedure**). The tricuspid atresia so created can further be repaired with first Glenn operation and then modified Fontan operation. In older children, treatment consists in controlling the supraventricular dysrhythmias followed later by repair of the valve or its replacement.

Prognosis

It is bad in case of neonates with overt signs and symptoms. In case of patients with mild anomaly, survival well into adulthood is usual.

EISENMENGER SYNDROME (Eisenmenger Complex)

The association of severe pulmonary arterial hypertension with reversal of the shunt through VSD is called the **Eisenmenger complex**. The term **Eisenmenger syndrome** denotes severe pulmonary arterial hypertension with reversal of shunt at the arterial, ventricular or pulmonary arterial level.

Clinical Features

- **Manifestations** include cyanosis, dyspnea, fatigue and dysrhythmias. With progression of the disease, the subject may go into heart failure and develop chest pain, syncope and hemoptysis.
- **Examination** shows presence of cyanosis (differential in PDA) and clubbing and a palpable pulmonary artery pulsation at left upper sternal border (parasternal impulse) and palpable second heart sound—pointing to development of pulmonary arterial hypertension. Auscultation reveals a loud narrowly split second heart sound and a soft ejection systolic murmur along left sternal border. A Graham Steell murmur (blowing diastolic murmur as a result of incompetence of pulmonary valve) may be audible along left sternal border.

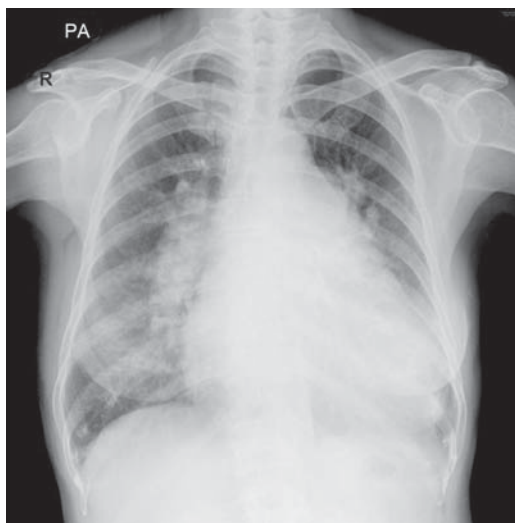


Fig. 27.15: Chest X-ray in Eisenmenger complex. Note that the findings are those of pulmonary artery hypertension, i.e. cardiomegaly, prominent pulmonary arterial segment, large main pulmonary arteries and their branches and hilar area plethoric and lung periphery oligemic. Abbreviation: PA, pulmonary artery.

Diagnosis

- **X-ray chest (Fig. 27.15)** shows findings of pulmonary hypertension
 - Heart size varying from normal to quite big, depending on the underlying condition.
 - Prominent pulmonary arterial segment.
 - Large main pulmonary arteries and their branches.
 - Hilar area plethoric and lung periphery oligemic.
 - **Electrocardiography** usually shows RVH but biventricular hypertrophy may occur. P wave may be tall and spiked (P pulmonale).
- **Echocardiogram** reveals a thick-walled right ventricle with, usually, increased dimensions of the chamber. Pre-ejection period/ejection time ratio is increased.
- **Cardiac catheterization** reveals a bidirectional shunt at the site of defect.

Treatment

Treatment is purely symptomatic. Frequent venesections with volume replacement may reduce polycythemia. Surgery is contraindicated.

Prognosis

It is a serious condition, carrying poor prognosis.

Prevention

This should be addressed to prevention of pulmonary vascular obstructive disease by early detection and treatment of CHD accompanied by increased pulmonary blood flow. An operation by 2–3 months and medical measures for pulmonary hypertension may be helpful.

TRANSPOSITION OF THE GREAT ARTERIES

It is the most important cause of cyanosis right at birth or soon after it. Also, it is responsible for most of the mortality from cyanotic CHD in the first year of life.

Transposition of the great arteries (TGA) occurs predominantly in males (four times more than in females). Incidence of diabetes in their grandparents is significantly high. Also, these babies are of relatively large birth weight, though they gain poorly in subsequent months.

Transposition of the great arteries is subdivided into complete type and physiologically corrected type. The complete type of TGA is further classified into TGA with VSD and TGA with intact ventricular septum. TGA with VSD is further subdivided into two groups based on the presence or absence of pulmonary stenosis. TGA with VSD and pulmonary stenosis is similar to TOF.

In physiologically corrected TGA, the right atrium is connected to an inverted morphologically left ventricle, which is connected to the pulmonary artery. Left atrium is connected to the inverted morphological right ventricle connecting to the aorta. Thus, the left ventricle gives a rise to pulmonary artery and right ventricle to aorta. This leads to normal root of blood. Nevertheless, almost all cases (98%) have associated anomalies (e.g. VSD, Ebstein anomaly, A-V conduction defects) which determine the clinical picture. It is best diagnosed by echocardiography showing ventricular inversion and associated anomalies.

Hemodynamics

In TGV, aorta arises from the right ventricle and the pulmonary artery from the left ventricle. The blood from right side of heart flows to aorta and the pulmonary venous blood is returned to lungs.

With the exchange of origins between aorta and pulmonary artery, the systemic venous blood by aorta from right side of heart flows to aorta and is recirculated in the systemic circulation, and oxygenated venous blood from the left side to the pulmonary artery and is recirculated in the lungs. Thus, with these two independent circuits, life can only be maintained postnatally if some communication between systemic and pulmonary circulation exists. Such a communication is usually provided by VSD, ASD, PDA or collateral circulation. It is the 'mixing' between the two circulations that decides the survival.

An associated VSD of a moderate size allows good mixing, leading to heart failure and pulmonary venous hypertension in second or third month of life. In case of a large VSD, pulmonary vascular obstructive disease (Eisenmenger physiology) develops early in life.

When atrial communication (small foramen ovale) is the mixing site, the infant becomes cyanotic along with heart failure and dyspnea immediately after birth (invariably in first week) as a result of severe hypoxemia and systemic acidosis.

Clinical Features

Severe cyanosis (differential with legs being less cyanotic than the arms), appearing at or shortly after birth, constitutes the hallmark of TGV. Later, dyspnea, heart failure and growth failure occur. Clubbing also develops in few months.

Heart is always enlarged. Murmurs are not of a classical pattern and are usually related to the type of

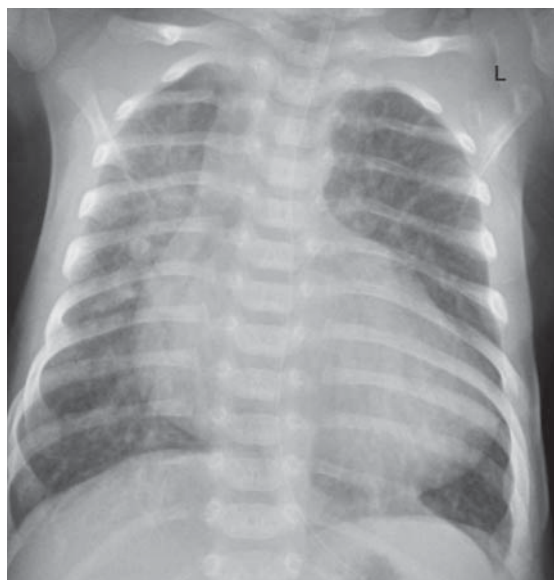


Fig. 27.16: Chest X-ray of transposition of the great arteries. Note the characteristic egg-on-side appearance with oligemic lung fields.

coexisting communication. Auscultatory findings in TGA with interatrial mixing who are symptomatic at birth with cyanosis include normal first heart sound, single second heart sound and an ejection systolic murmur (grade 1–2) which has no significance.

Auscultatory findings in TGA with VSD, who develop heart failure, cyanosis, and cardiomegaly in second or third month of life, are normal first heart sound, single or normally split second heart sound and grade 2–4 ejection systolic murmur, apical third sound gallop or a mid-diastolic rumble.

Diagnosis

- **Chest X-ray** shows enlarged heart with a narrow base (pedicle) on account of malposition of great vessels and grossly plethoric lung fields (more so in the upper portion) and often absent thymic shadow. Egg-on-side appearance is characteristic (Fig. 27.16).
- **Electrocardiography** reveals RVH, right axis deviation and often P pulmonale.
- **Echocardiography** (Fig. 27.17) confirms the diagnosis. It shows equal peak systolic pressure in both ventricles, aorta and pulmonary artery.
- **Cardiac catheterization** and **selective angiography** help in confirming the diagnosis.

Treatment

- Medical treatment with IV prostaglandin E1 (PGE1) for keeping PDA open, digoxin, diuretics, iron, etc. should be given as and when indicated.
- For an interim palliation (temporary relief), a **balloon septoplasty** under echocardiography in second or third month of life may be performed to attain improved mixing.
- Of the various surgical procedures, currently best is the arterial switch operation which should be performed early enough, i.e. within 2–4 weeks of life.

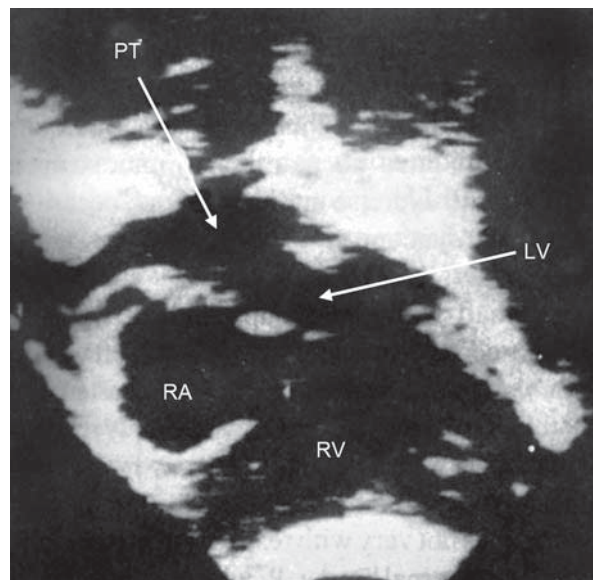


Fig. 27.17: Echocardiography (two-dimensional) in transposition of the great arteries.

Abbreviations: RV, right ventricle; LV, left ventricle; RA, right artery.

Here, distal aorta is anastomosed with the proximal pulmonary stump (neo-aortic root) and pulmonary artery with the proximal aortic stump (neo-pulmonary artery). **Beffe's operation** seems to offer the best results. It consists in partial redirection of venous blood, i.e. vena caval anastomosis to the left atrium and pulmonary veins to the right atrium. This operation gives over 90% 20-year survival.

TOTAL ANOMALOUS PULMONARY VENOUS RETURN

(Total Anomalous Pulmonary Venous Connection)

In this uncommon cyanotic CHD, pulmonary veins fail to join left atrium and, instead, are connected anomalously so that total pulmonary venous blood reaches right atrium. It may be of supracardiac, cardiac, infracardiac or mixed type. Infracardiac total anomalous pulmonary venous return (TAPVR) is always obstructive. Nonobstructive type is more frequent. In both types, there is a mixing of oxygenated and deoxygenated blood before or at the level of the right atrium.

Hemodynamics/Pathophysiology

As a consequence of both pulmonary venous blood as well as systemic venous blood entering the right atrium, two venous returns show nearly total mixing. Two sequels of such a mixing are—(1) Oxygen saturation in the pulmonary artery and aorta may be nearly identical, (2) Left atrium receives blood from right ventricle through foramen ovale/ASD (right-to-left shunt).

Clinical Features

Manifestations include three patterns:

1. **First:** Severe tachypnea, cyanosis and moribund state in neonates with severe obstruction.

- 480 2. **Second:** Heart failure (without cyanosis) early in life with gallop rhythm and murmurs along the left sternal border, pulmonary hypertension when obstruction is only slight or moderate.
3. **Third:** Absent or mild cyanosis in infancy; there is absolute mixing of pulmonary venous blood with a large left-to-right shunt.

Diagnosis

- Chest X-ray shows **figure of eight** or **snowman** configuration with a characteristic supracardiac shadow (Figs 27.18 and 27.19).
- **Electrocardiography** shows RAD and RVH. In case of severe obstruction, P pulmonale may be seen.
- **Echocardiography** shows a venous channel in abdomen and flow away from heart is pathognomonic of TAPVR.

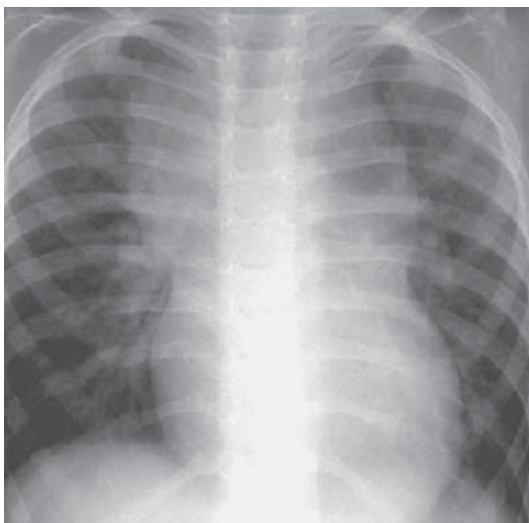


Fig. 27.18: Chest X-ray in total anomalous venous return showing **figure of eight** or **snowman** appearance. Head of snowman is made of superior mediastinal shadow formed by SVC on right side, vertical vein on left side and left brachiocephalic vein superiorly. Body of snowman is the heart. Sometime termed **snowman in snowstorm** in which snowstorm refers pulmonary plethora.



Fig. 27.19: Diagrammatic representation of radiological appearance in total anomalous pulmonary venous return. Note the **snowman** or **figure of eight** configuration.

Treatment

Treatment is surgical correction at the earliest preceded by stabilization with (PGE1) so that ductus venosus and ductus arteriosus are dilated.

Prognosis

Without treatment, most subjects with TAPVR succumb to heart failure within 3 months of life. Prognosis following surgery is good. Some cases of obstructed TAPVR may develop pulmonary hypertensive crisis in postoperative period; others may be complicated by progressive pulmonary venous obstruction.

HYPOPLASTIC LEFT HEART SYNDROME

The syndrome refers to the presence of obstructive lesions (vascular or valvular) on the left side of the heart, leading to hypoplasia of the left ventricle. It is by no means uncommon.

Hemodynamics

In all the lesions that make this syndrome, namely mitral atresia, aortic atresia or stenosis, gross obstruction to either filling or emptying of the left ventricle during intrauterine life leads to a very small amount of blood in the left ventricle. As a result, the left ventricle becomes hypoplastic. After birth, two factors (obstructive lesions and hypoplastic left ventricle) join hands in impairing the circulation, resulting in CCF, usually within some days but always before the age of 3 months.

Clinical Features

Congestive cardiac failure develops fairly early, particularly in subjects with aortic atresia in whom it may occur as early as in the first week of life. In aortic involvement, cyanosis may be differential, but it is usually generalized in most cases of this syndrome. Murmurs, if present, are usually nonspecific and not diagnostic.

Diagnosis

Right at birth, **X-ray chest** is normal, but soon it reveals progressive cardiomegaly with plethoric lung fields. **Electrocardiography** changes include right axis deviation, right atrial hypertrophy, RVH with relative paucity of left ventricular forces and absence of Q wave in V6. **Echocardiography** shows a diminutive aorta and left ventricle with a poorly defined mitral valve in the presence of a normal and easily definable tricuspid valve. These findings are diagnostic.

Treatment and Prognosis

Currently, no effective treatment is available. CCF is the rule. Death occurs very early in aortic involvement and relatively late in mitral atresia. A few patients have lived a decade or so.

AORTIC STENOSIS

Depending on the site of obstruction to the outflow of blood from the left ventricle in relation to the aortic valve, congenital aortic stenosis may be divided into—valvular,

subvalvular (subaortic) and supralvalvular (William syndrome). Valvular stenosis accounts for 75% of the cases of aortic stenosis. Subvalvular stenosis is of three types—(1) discrete membranous, (2) fibromuscular and (3) idiopathic hypertrophic.

Hemodynamics

Obstruction to the left ventricular outflow as a result of aortic stenosis increases the load of left ventricle. This is accomplished by raising the systolic pressure inside it and by its hypertrophy. An aortic valve of less than $0.5 \text{ cm}^2/\text{m}^2$ body surface area or a pressure gradient of more than 70 mmHg across aortic valve is regarded as severe obstruction.

Clinical Features

Most patients have no manifestations, except easy fatigability and exercise intolerance and, occasionally, dizziness and syncope.

- In **valvular aortic stenosis**, pulses are normal but may be small with a slow upstroke, if the pressure gradient exceeds 80 mmHg. Apex shows left ventricular thrust and a systolic thrill at right base, suprasternal notch and both carotid arteries (in mild disease only right carotid artery) may be found.
- **Auscultatory findings** include
 - A prominent ejection click that does not vary with respiration at the aortic area and lower left sternal border,
 - P2 which is physiologically split, and
 - A grade 3 to 4/6 rough, medium to high-pitched ejection systolic murmur which is best heard at the first and second spaces and is radiated to suprasternal notch and the carotids, as also down the left sternal border and the apex
- In **discrete membranous subvalvular aortic stenosis**, the clinical findings are essentially the same but there is no ejection click and a diastolic murmur of aortic regurgitation is usually present after the age of 5 years.
- **Fibromuscular subvalvular aortic stenosis** is clinically almost impossible to differentiate from the discrete membranous type.
- **Idiopathic hypertrophic aortic stenosis (IHAS)** too does not show any ejection click. The ejection systolic murmur (grades 2 to 3/6) is heard over the left sternal border and the apex. A murmur of mitral regurgitation usually accompanies it.
- In **supralvalvular aortic stenosis**, the patient has characteristic **elfin facies** with prominent forehead, epicanthal fold, widely set eyes, depressed bridge of nose, overhanging lip, deformity of teeth, strabismus, and mental retardation. It may coexist with metabolic disorders like idiopathic hypercalcemia and hypervitaminosis D, leprechaunism and Williams syndrome. The condition is often familial. The cardiac findings include the thrill and, murmur which are best found in the suprasternal notch and along the carotids. The pulse and systolic pressure in the right arm is higher than in left arm.

Diagnosis

- **X-ray chest** shows somewhat prominent left ventricle, though heart size is usually within normal limits. Dilatation of aorta suggests valvular and, sometimes, discrete membranous subvalvular stenosis.
- **Electrocardiography** is normal in mild disease. In severe obstruction, the changes include LVH and strain which may be progressive and left ventricular strain which warns that operative intervention is warranted.
- **Echocardiography** is of value in the diagnosis and follow-up of IHAS and other types of the disease.
- **Serial catheterization** may well be the only dependable guide to the progression of the disease.
- **Cineangiography** assists in demonstrating the exact site of the stenotic lesion.

Treatment

The patient should have close follow-up. He should be discouraged from overexertion, i.e. competitive sports, athletics and strenuous exercise in the presence of a gradient more than 50 mmHg. Valvular aortic stenosis with a resting gradient more than 75 mmHg is best treated by balloon aortic valvuloplasty. Supralvalvular and subvalvular aortic stenosis needs aortic valvotomy, and aortic valve replacement with a prosthetic valve.

Unfortunately, surgery in the form of valvotomy may be complicated by aortic regurgitation which is worse than the stenosis. The patient who gets valve replacement has got to be on anticoagulants. Secondly, neither the prosthetic nor the homograft valve lasts indefinitely. The results of surgery in discrete membranous subvalvular aortic stenosis are better than in valvular.

COARCTATION OF AORTA SYNDROME

The coarctation or constriction may be distal to the ligamentum or ductus arteriosus or the subclavian artery (postductal), or proximal to them (preductal). The constriction is in the shape of a sharp indentation involving the anterior, lateral and a posterior wall of the aorta. The aorta immediately distal to the coarctation is often dilated.

The term **coarctation of aorta syndrome** is now regarded as a better nomenclature since many symptomatic patients, particularly infants, are likely to have such accompaniments as VSD, PDA, tubular hypoplasia of the aortic isthmus and bicuspid aortic valve. The disease occurs thrice more frequently in males than in females. It is a common association in Turner syndrome.

Hemodynamics

In the so-called **preductal (infantile) type**, the very high load on the left ventricle causes elevation in both systolic and diastolic pressures. Since there are no collaterals because of the situation of the coarctation, the infant becomes immediately symptomatic with CCF.

In the so-called **postductal (adult) type**, there is development of collaterals connecting branches of the

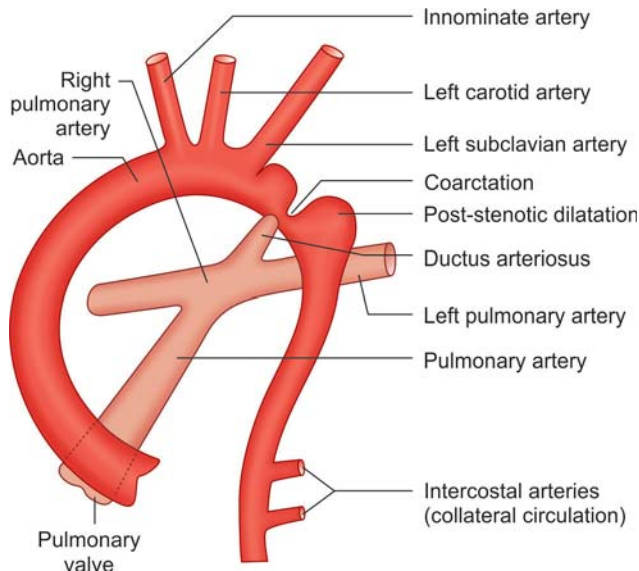


Fig. 27.20: Adult (postductal) type of coarctation of aorta. Note the collaterals which spare the infant from left ventricular failure.

subclavian artery to the arteries which arise from the aorta. The distal level of coarctation spares the infant from developing ventricular failure (Fig. 27.20).

Clinical Features

In severe cases, usually of preductal type, the infant may present with CCF in first 1–3 weeks. **Manifestations** include feeding difficulty, dyspnea, FTT, pitting edema, gallop rhythm and rarely differential cyanosis due to the PDA. Heart murmurs, depending on the associated cardiac conditions such as VSD, may be heard. A systolic murmur is usually found over the interscapular area. In postductal type, manifestations developing in later childhood may include fatigue, cramps, intermittent claudication, headache, weakness and exertional dyspnea. In some cases, overgrowth of upper limbs and chest may occur.

The most dependable physical finding is the weak, delayed and even absent femoral arteries compared to the strong brachial arteries. The blood pressure in the arms is much higher than in the legs (this observation is of significance only after 1 year of age). Occasionally, due to involvement of the left subclavian artery, left brachial pulse may be weaker and the blood pressure in the left arm is lower than on the right side. Dilated and tortuous collaterals may be seen over the interscapular area in older children. It is called **Suzman sign**.

In uncomplicated coarctation, an ejection systolic murmur (grade 2/6) is heard at the aortic area and the lower left sternal border. A systolic murmur in the interscapular area is considered pathognomonic of the coarctation.

Diagnosis

- **X-ray chest** findings include some left ventricular enlargement, notching of the ribs caused by intercostal collaterals and 'E' sign on barium swallow. The first arch of the 'E' is due to dilatation of aorta before the coarctation, the second due to poststenotic dilatation and the middle due to the coarctation *per se*.

- **Electrocardiography** may be normal or suggestive of RVH, particularly in infants.
- **Echocardiography** (real-time two-dimensional) may visualize the coarctation directly. Only indirect evidence of coarctation may be forthcoming from the M-mode echocardiography.
- **Cardiac catheterization** and **angiocardiography** demonstrate the location and severity of the coarctation and the adequacy of the collaterals.

Treatment

Medical management consists in tackling heart failure and hypertension, dilatation of the associated PDA with a constant infusion of prostaglandin E1 in critical situations, and restriction of strenuous exercise. Antibiotic prophylaxis against bacterial endocarditis is desirable. Balloon dilatation may be done as an interim palliative measure as soon as diagnosis of severe coarctation of the aorta is made.

The best age for surgery is 3–5 years, provided that significant systemic hypertension has not developed. Corrective surgery consists of resection of the segment of coarctation and end-to-end anastomosis, using a dacron graft or, preferably, subclavian flap. With the latter, chances of development of re-coarctation in later life are considerably reduced.

Prognosis

- If heart failure develops in neonatal period or early in infancy, death is a rule unless vigorous treatment is offered.
- If the infant survives, he may do well without surgery for some years.
- If no heart failure occurs during the neonatal period or early infancy, the child may do well without surgery throughout childhood and adolescence.
- Hypertensive cardiovascular disease and encephalopathy, bacterial endocarditis and, intracranial bleeding may prove fatal complications. Re-coarctation of aorta may warrant repeat balloon angioplasty.

PULMONARY STENOSIS

It may be valvular, subvalvular (infundibular) or supraventricular.

Hemodynamics

Forcing blood flow across the stenotic pulmonary artery causes RVH (concentric) with heart of reduced distensibility but normal size.

Clinical Features

Mild pulmonary stenosis is asymptomatic. Manifestations of moderate–severe pulmonary stenosis include palpitations, easy fatigability and exercise intolerance/exertional dyspnea and cyanosis in neonates.

Auscultatory findings include an ejection systolic murmur at second left intercostal space with radiation to the back. S2 may be widely split with a quiet pulmonary component. A thrill may be present. An impulse at the

lower left sternal border points to a severe stenosis. A click varying with respiration points to a valvular stenosis. An increase in the duration of the murmur and a higher frequency of the sound are signs of worsening stenosis.

Diagnosis

- **Chest X-ray** shows dilation of the main pulmonary artery (post-stenotic dilatation) in moderate-severe stenosis.
- **Electrocardiography** shows right axis deviation and RVH in moderate-severe stenosis. P pulmonale suggests severe stenosis.
- **Echocardiography** provides such vital information as the exact site of stenosis, degree of RVH, valve morphology and pressure gradient.

Treatment

Balloon valvuloplasty is the first choice in symptomatic/severe pulmonary stenosis for reducing the gradient to acceptable levels. Surgical repair is indicated in the (1) event of failure of balloon valvuloplasty and, (2) in subvalvular (muscular/infundibular) pulmonary stenosis.

CONGENITAL HEART DISEASE AND NEUROLOGIC COMPLICATIONS

Congenital heart disease may be accompanied by developmental anomalies elsewhere. In addition, it is vulnerable to several acquired neurologic complications. Cardiac surgery in CHD involves intricate procedure employing a cardiopulmonary bypass and/or total circulatory arrest. Such stressful events can further cause various neurologic complications (Box 27.9).

Whereas early (before the first birthday) operative surgery on CHD considerably safeguards from development of neurologic complications preoperatively, special action is required to be taken to prevent complications arising out of the surgery. Some of the strategies developed to minimize central nervous system (CNS) injury from surgery for CHD include:

Box 27.9 Neurologic complications of congenital heart disease

- Accompanying developmental neurologic anomalies
- Acquired neurologic lesions

Preoperative

- **Chronic hypoxia:** Impaired cognitive outcome
- **Global ischemia:** Poor systemic perfusion or intense erythrocytosis with high hyperviscosity causing seizures, disorientation or excessive irritability
- **Acute focal ischemia:** Cerebrovascular accident from arterial or venous thrombosis, paradoxical embolization, direct embolization
- **Infections:** Brain abscess, infective endocarditis causing mycotic aneurysms

Intraoperative/Postoperative

- Hypoxic-ischemic encephalopathy
- Seizures
- Stroke
- Movement disorders.

- Minimum use of circulatory arrest.
- Use of pH-stat technique during hypothermic bypass.
- Avoidance of post cardiopulmonary bypass hypothermia.

RHEUMATIC FEVER/RHEUMATIC HEART DISEASE

Rheumatic fever, a disease state that occurs following a streptococcal throat infection, is an important cause of acquired heart disease in children. It can be defined as a post-streptococcal immune-mediated disorder occurring as a result of cross-reaction between the connective tissue of the body and the antibodies produced against streptococcal cell wall proteins, and sugars. The result is a varied combination of specific clinical features which constitute rheumatic fever.

Epidemiology

The incidence of rheumatic fever is closely related the incidence of group A streptococcal pharyngitis. It is more common in developing countries than in developed countries. Though the disease has been controlled in the Western countries by improved sanitary measures and primary prevention, it has recurred in recent times. The reported incidence in these countries is 0.3% of general population. In the crowded population, the incidence is about 1–3%. Rheumatic heart disease is the only sequelae of rheumatic fever. An Indian Council of Medical Research Survey had recorded an incidence of 5.3/1,000 children aged between 6 years and 16 years. Recent surveys have shown a remarkable fall in its incidence from 5.3 to 0.5–1/1,000.

Rheumatic fever is more common in the age group of 5–15 years. Both the sexes are equally affected, although the sequelae of the disease, mitral stenosis and chorea, are more common in females. However, aortic regurgitation is more common in boys.

Various predisposing factors are poor socioeconomic status, overcrowding (orphanages, military recruits, etc.) and unhygienic living conditions. It is more common during fall, winter and early spring, coinciding with increased incidence of streptococcal infections.

Etiopathogenesis

Despite significant improvement in understanding of the disease in recent times, the etiopathogenesis of rheumatic fever is not clear. However, the available data suggest that it occurs following group A beta-hemolytic streptococcus throat infection. The observations, preceding streptococcal throat infection as evidenced by the markers of streptococcal infection, seasonal variations of the rheumatic fever coinciding with increased incidence of streptococcal throat infection and effectiveness of penicillin prophylaxis in preventing the rheumatic recurrence suggest association with group A streptococcal throat infection. However, the organism has not been isolated from joints, blood or the heart.

484 The hypotheses postulated to explain the pathogenesis of rheumatic fever following streptococcal infection include toxic effects of the extracellular toxins of the organism and an abnormal immune response. The available data do not support possible toxic effect of the toxins on the human target organs. On the other hand, abnormal immune response of the human host to some still unidentified components of group A streptococcus is more accepted as a possible pathogenic mechanism. The occurrence of the rheumatic fever after a latent period following streptococcal throat infection gives credence to the immune-mediated mechanism. This hypothesis is further supported by the observations that group streptococcal M proteins share certain amino acid sequence with some human hosts. M proteins of the organism are the virulence factor, and it is responsible for the organism's ability to result in the phagocytosis. The similar amino acid sequence in some individuals has been thought to be responsible for cross-reaction between the organism and its human host. The presence of common antibodies to the antigens found in the group A streptococcus cell membrane, in the caudate nucleus of the brain in patients with Sydenham's chorea further support the abnormal autoimmune mechanism responsible for central nervous system manifestations of rheumatic fever. The susceptibility of the human to the risk of rheumatic fever is not same in all individuals. Increased susceptibility for the development of rheumatic fever and subsequent rheumatic heart disease among certain high-risk individuals suggest possible genetic predisposition. This is supported by the presence of a specific alloantigen on the surface of non-T lymphocytes in 70–90% of individuals with rheumatic fever compared to fewer than 30% of non-rheumatic individuals. The marker was found to be more common in families of rheumatic individuals. The reason for this is not known. Human leukocyte antigen (HLA) studies suggest an association with HLA-DR3.

Clinical Features

No specific clinical manifestation or laboratory test unequivocally establishes the diagnosis of rheumatic fever. Hence, set criteria for making the diagnosis have been laid down. These modified Jones criteria 7 (revised) as per Table 27.7 are currently followed all over the world to make clinical diagnosis of rheumatic fever. The guidelines include major criteria, minor criteria and essential criteria. Major criteria are basically the major and common clinical features of rheumatic fever. Minor criteria are supportive of rheumatic fever in the presence of some major criteria. However, the most important aspect of this guideline is the necessity of having an essential or a definitive evidence of preceding streptococcal infection. Two major or one major and two minor criteria, in the presence of essential criteria are required to make the diagnosis of acute rheumatic fever.

The typical clinical picture of rheumatic fever is that a child suffers from streptococcal throat infection, which

Table 27.7: Modified Jones criteria (revised) for the diagnosis of rheumatic fever

Major	Minor
<ul style="list-style-type: none"> • Carditis • Polyarthritits (Migratory) • Chorea • Subcutaneous nodules • Erythema marginatum 	<p><i>Clinical</i></p> <ul style="list-style-type: none"> • Fever • Arthralgia • Previous rheumatic fever or rheumatic heart disease <p><i>Investigative</i></p> <ul style="list-style-type: none"> • Prolonged P-R interval in the ECG • Increased ESR or presence of C-reactive proteins (CRP)
<p>Essential criteria Evidence of preceding group A streptococcal infection (culture, rapid antigen, antibody rise/elevation).</p>	

improves either spontaneously or with treatment. One to few weeks later, the child develops fever along with other clinical features of rheumatic fever. The guidelines are meant for making a correct diagnosis as it has prognostic and therapeutic implications. However, in exceptional situation, the diagnosis can still be considered without fully satisfying the criteria. These exceptions for diagnosing rheumatic fever are chorea, insidious or late onset carditis and rheumatic recurrence.

As chorea is a late manifestation, the other features of rheumatic fever may not be present along with it. In the absence of other causes, it can be considered rheumatic chorea. Even the requirement of preceding streptococcal infection can be ignored. Similarly, insidious or late onset of carditis can be considered as rheumatic carditis, provided other causes are ruled out. In this case too, requirement of preceding streptococcal infection can be ignored. About rheumatic recurrence, in patients with documented rheumatic heart disease or prior rheumatic fever, the presence of one major criteria or of fever, arthralgia, or elevated acute phase reactants suggest a presumptive diagnosis of recurrence. However, the evidence of preceding streptococcal infection is necessary.

Major Criteria

Carditis

Carditis is one of the major criteria. Rheumatic carditis is basically a pancarditis involving endocardium, myocardium and pericardium. It occurs in 50–60% of patients with acute rheumatic fever. It is an early manifestation with most of the patients developing carditis within first two weeks of life. Involvement of all three structural components of the heart results in clinical manifestation of either all or any one or two of the components. However, the common manifestations of rheumatic fever are due to involvement of the endocardium. The clinical manifestation of endocardial involvement is basically valvular insufficiency. The most commonly affected valve is mitral valve. Most often, it is affected alone and, in some cases, it occurs in combination with aortic valves. Isolated aortic valve involvement is rare. Tricuspid and pulmonary valve involvement is unusual. Rheumatic carditis is either mild or severe and the clinical features depend upon the severity. The clinical features

include pansystolic murmur of mitral insufficiency, apical mid-diastolic murmur or basal diastolic murmur. If tricuspid regurgitation is present, a low-grade holosystolic murmur is heard along lower left sternal border. In severe carditis, acute volume overload on the left ventricle can result in left ventricular failure. Heart failure is the major cause of mortality in acute rheumatic fever. Myocarditis of acute rheumatic fever presents with soft first heart sound, S3 gallop, CCF, Carey coombs murmur and cardiac enlargement. The features suggestive of pericarditis include pericardial chest pains, pericardial rub and may have minimal effusion.

Carditis is an important manifestation of acute rheumatic fever and it is the only acute manifestation that results in chronic changes. It predisposes to the only sequelae of the acute rheumatic fever, rheumatic heart disease. Chronic changes result in scarring of the valves and even calcification of the valves in the long run and result in stenosis.

Polyarthritis

It is an early manifestation and occurs in 70–75% of cases. Rheumatic arthritis is a polyarthritis. It is the most confusing among the major criteria and results in more diagnostic error than any of the other manifestations. It is a migratory polyarthritis involving the large joints, like knees, ankles, elbows and wrists. It rarely involves small joints, like fingers, toes, or spine. The arthritis of rheumatic fever is exquisitely tender. The joints are swollen, red, severely tender and movements are limited. In an untreated case, symptoms usually last about a week. The arthritis does not result in chronic joint disease or destruction. If anti-inflammatory drug therapy is initiated, the signs and symptoms disappear rapidly in 12–24 hours. This is a therapeutic approach, which helps in diagnosing and differentiating rheumatic arthritis from other causes of arthritis. If patient does not respond to the anti-inflammatory therapy, it is unlikely to be rheumatic arthritis. Prior anti-inflammatory therapy may eliminate the classical migratory nature of the polyarthritis. Joint effusion may occur and the joint aspiration shows polymorphonuclear leukocytosis. However, it is a nonspecific finding and not essentially required.

Rheumatic (Sydenham's) Chorea

It is a late manifestation of rheumatic fever, occurring much later than the other manifestations. It usually occurs about 3 months after the acute rheumatic fever. The choreoathetoid movements may begin very subtly, making the early diagnosis difficult. Early manifestations include clumsiness, and it can be elicited by enquiring from the parents and children.

In school going children, deterioration of the handwriting is the best sign suggestive of chorea (Fig. 27.21). The characteristic chorea movement consists of purposeless, jerky movements resulting in deranged speech, muscular incoordination, awkward gait and weakness. Emotional lability is usually seen and child may develop depression also. As a result of chorea, the child may not be

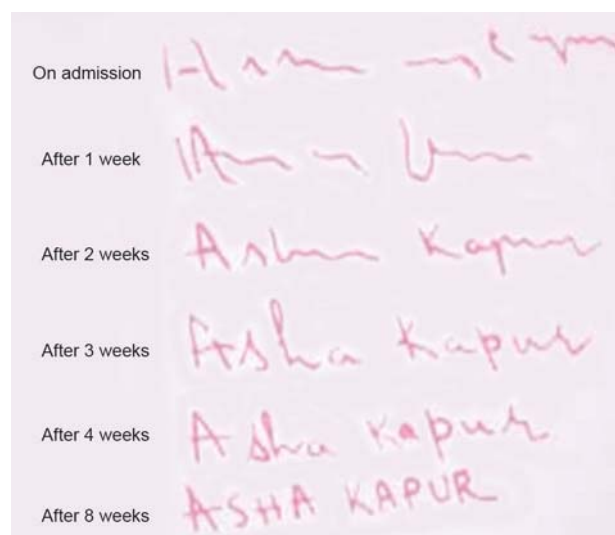


Fig. 27.21: Serial writings on hospitalization and during the course of recovery of a 13-year-old convent-going girl suffering from rheumatic chorea.

Box 27.10

Various tests for the diagnosis of rheumatic (Sydenham's) chorea

- Finger-nose test
- Buttoning the clothes test
- Dinner-fork posturing of the outstretched hands (Fig. 22.23)
- Pronator test: Pronation of forearm when the hands are raised above the head (Pronator test)
- Milkmaid grip—alternating relaxation and tightening of handshake
- Darting tongue—tongue keeps moving like a 'bag of worms' on protruding
- Audible clicks during speech
- Clumsiness or inability in clear, organized writing (Fig. 22.21)
- Ataxia
- Counting the digits test
- Sustained hung-up or double knee jerk.

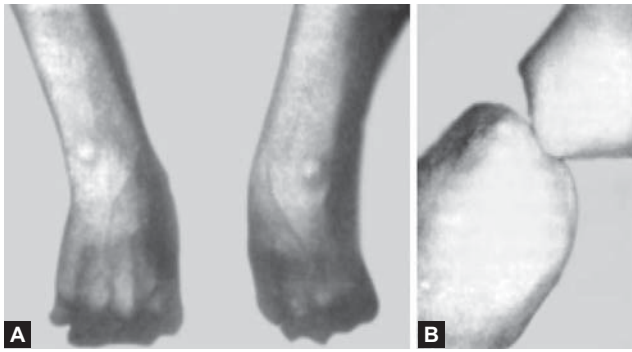
able to carry on schooling and some daily work. Chorea is usually self-limiting disorder. Untreated it subsides in few weeks to a month or more. Recurrences are known. It is important to differentiate Sydenham's chorea from other movement disorders and also to rule out other causes of chorea. It is an exception to the diagnosis of acute rheumatic fever without satisfying all the criteria necessary for the diagnosis (Box 27.10).

Subcutaneous Nodules

Subcutaneous nodules are a late manifestation. They are seen in about 3.5% of cases and usually appear around 6 weeks. Though infrequent, they are more likely to be observed in patients with severe carditis. Subcutaneous nodules are pea-sized, firm and nontender nodules. They appear on bony prominence, like knees, elbows, shins, over the spine and occiput. They disappear in few days to weeks. They are better palpated than seen (Figs 27.22A and B).

Erythema Marginatum

It is a very infrequent finding and difficult to diagnose. It may start as a nonspecific pink macules over the trunk.



Figs 27.22A and B: Rheumatic (subcutaneous) nodules. Besides over the extensor surface of wrist, elbow and knee joints, these shot-like hard bodies may be detected in occipital region or over spinous processes of thoracic and lumbar vertebrae.



Fig. 27.23: Dinner-fork sign in rheumatic chorea. Note the flexion at the wrist and extension of the fingers in the typical chorea hands.

With the appearance of more rashes, they spread and fuse each other to form a serpiginous outline. It is a non blanching, evanescent rash and difficult to identify in individuals with dark complexion.

Minor Criteria

Minor criteria include both clinical and laboratory parameters. They are less sensitive and specific and, hence, they are just contributory findings in the diagnosis.

Fever

It is seen in almost all cases of acute rheumatic fever, and usually it is of mild-to-moderate grade. However it is very nonspecific and could be a manifestation of any other infection.

Polyarthralgia

Pain in joints without any other signs of inflammation, like fever, is very nonspecific. It should not be used as a minor criterion when polyarthritis is included as a major criterion.

Laboratory Manifestations

These include elevated erythrocyte sedimentation rate (ESR), and positive C-reactive protein and prolonged PR

interval. ESR is raised in all patients with acute rheumatic fever and it remains for a prolonged period. Similarly C-reactive protein is also elevated in all patients. Prolonged P-R interval on electrocardiogram is also a nonspecific finding and may occur in many conditions. There can be evidence of varying degrees of heart block also. However, complete heart block is extremely rare in acute rheumatic fever.

Essential Criteria

This is the cornerstone of modified Jones criteria. All other criteria are built around it. The preceding group A streptococcal infection is documented by either positive throat culture, a history of scarlet fever or elevated streptococcal antibodies. Among them, the most reliable is estimation of antibodies against the group A streptococci.

- Various antistreptococcal antibodies are antistreptolysin O (ASO), antihyaluronidase (AHD), antideoxyribonuclease (AD), streptokinase antibodies and many others. ASO is the commonly used antibody test. ASO titers are significantly raised following an acute group A streptococcal infection. Drawbacks of ASO titers is that it only suggest whether there was a preceding group A streptococcal infection or not and nothing else. High titers are considered more significant in making the diagnosis, but low titers do not exactly rule out the diagnosis. Rising titers of ASO is a strong evidence of a recent streptococcal infection than a single titer result. The ASO titer reaches its peak by 3–6 weeks.
- Positive throat swab culture is the gold standard for confirmation of the presence of groups A streptococcal infection. All patients with acute rheumatic fever should have at least one throat swab culture before the initiation of antibiotics. The drawback of positive throat swab culture include low positive results due to improper sample collection and storage, prior antibiotic therapy, and it only suggests whether there was a throat infection or not. It could be positive even in an individual without the evidence of acute rheumatic fever.

Other Investigations

- **Chest roentgenogram** may show evidence of cardiomegaly. Nonspecific elevations of gamma globulin may be seen. There may be mild leukocytosis.
- **Role of echocardiography in acute rheumatic fever:** Though echocardiography findings has not been included in the criteria for diagnosing acute rheumatic fever, it has a major role to play in the diagnosis of subclinical and mild carditis cases which are usually missed on clinical examination. It also helps in assessing the severing of the cardiac abnormalities and subsequently in assessing and follow-up of patients with chronic valvular disease. It is also helpful in diagnosing carditis in rheumatic recurrence.

New Diagnostic Modalities

At least three new diagnostic modalities for confirming presence of carditis are now available (Box 27.11).

Box 27.11 Role of new modalities for confirming presence of rheumatic carditis

Modality	Remarks
Echocardiography	Of remarkable utility in diagnosing subclinical or mild carditis (mild valvular regurgitation) that is usually missed by clinical examination.
Artificial subcutaneous nodule	Appearance of artificial subcutaneous nodules 4–10 days after injection of auto-test logous blood is 100% specific but only 62% sensitive. The time lag of 4–10 days is its negative point for wide spread use.
Endomyocardial biopsy	A positive biopsy showing Aschoff nodules or histiocytes establishes the diagnosis but a negative biopsy (which is more often the case) does not rule out carditis. Hence, not quite useful as a routine diagnostic procedure.

Differential Diagnosis

Rheumatic fever has to be differentiated from various other disorders which can manifest with similar clinical features. These disorders include rheumatoid arthritis, viral arthritis, collagen vascular disorders (e.g. SLE), infective endocarditis, Lyme's disease, etc. Differentiating rheumatoid arthritis becomes more important when a patient presents with arthritis as a major manifestation. Differentiating from infective endocarditis is most crucial in the management of acute carditis. At times, it is very difficult, especially in cases of rheumatic recurrence in a case of preexisting rheumatic heart disease. Echocardiogram and blood culture are useful investigations in these situations.

Complications

The only complication and long-term sequel of acute rheumatic fever is rheumatic valvular heart disease.

Treatment

The treatment of acute rheumatic fever includes supportive therapy, treatment of clinical manifestations using anti-inflammatory drugs and treatment of group A streptococcal infection.

- **Bed rest:** All patients with acute rheumatic fever, especially the ones with carditis, should be advised strict bed rest till the symptoms are subsided. Ideally, the bed rest should be given for 6–8 weeks period, the period generally needed for rheumatic activity to subside. In the absence of carditis, however, patient can be ambulated earlier. Presence of CCF may require prolonged bed rest.
- **Diet:** Adequate proteins, vitamins and micronutrients should be supplemented. In the absence of carditis, there is no need for restricting the salt. Salt restriction may be required in the presence of CCF.
- **Anti-inflammatory drug therapy:** Anti-inflammatory agents are the mainstay in the management of acute rheumatic fever. These agents are required to suppress the ongoing inflammation and provide symptomatic relief. Salicylates and steroid are the drugs used.

- **Aspirin** is the drug of choice. Aspirin results in reduction in fever, pain and swelling of the joints dramatically. The joint symptoms disappear within 12–24 hours. The dose is 100 mg/kg/day in four divided doses. This dosage is expected to maintain a blood level of 20–25 µg/dL. If the facilities are available to estimate blood salicylate level, the dosage is adjusted to achieve and maintain this blood level.

When ESR comes to normal, 60 mg/kg/day should suffice. The total duration of therapy is about 12 weeks to completely suppress the inflammation. The full dosage should be continued for about 10 weeks and then tapered and stopped over next 2 weeks. When the patient is on aspirin therapy, it is very important to monitor for drug toxicity both clinically and by the estimation of blood salicylate levels. The earliest sign of salicylate toxicity is tinnitus. When patient complains of tinnitus, look for other manifestations of salicylism, stop the drug and ask for blood salicylate level. If patient develops toxicity, the dosage has to be reduced and continued with monitoring. No other anti-inflammatory drugs have been proved to be beneficial in the treatment of acute rheumatic fever.

- **Steroids therapy** in acute rheumatic fevers indicated in:

- Carditis with heart failure
- Severe carditis with impending heart failure.

Steroids are helpful in controlling the acute inflammatory process, but do not modify the incidence or severity of the residual chronic rheumatic heart disease. Generally steroid therapy is required for 4 weeks duration. Steroid that is most commonly used is prednisolone in a dose of 2 mg/kg/day, in divided doses. Introduce aspirin when the tapering of steroids starts, i.e. in the last week of steroid therapy. Continue aspirin for 9 weeks. This helps in preventing rebound rheumatic activity and also the adverse effects of prolonged steroid therapy. Approximately, a course of 12 weeks combined steroid–aspirin therapy (steroid 4 weeks, aspirin 9 weeks; 4th week common, i.e. overlap of steroid tapering and aspirin introduction) is required.

- **Treatment of heart failure:** CCF due to severe carditis requires aggressive treatment with drugs. Start with diuretics and use digoxin as and when required. Some patients may develop intractable heart failure, and they may not respond to even the additional medical therapy. In these cases, surgical therapy in the form of valve replacement with prosthetic valve or valvuloplasty may be required. It is important to remember that surgical treatment is an integral part in the management of acute rheumatic fever, though it is required rarely.
- **Treatment of chorea:** Reassure the parents that it is a self-limiting condition. Advise both physical and mental rest for some time. Consider using drugs if the symptoms are severe. The drugs used are phenobarbitone, chlorpromazine, diazepam and haloperidol. Start with phenobarbitone and consider using other drugs as required. Haloperidol is advised for severe cases only. However, it is necessary to watch for side effects.

There is no obvious role for aspirin or steroids, though some observers have documented better improvement on adding steroids into the treatment regimen.

- **Treatment of group A streptococcal infection:** Take throat swab samples for culturing and start the patient on penicillin therapy. This is to eradicate the streptococcal infection. Procaine penicillin–400,000 units, intramuscularly, twice daily, for 10 days is necessary. Alternatively use oral penicillin 4 lakh units (250 mg), every 4–6 hourly for 10 days. After the completion of the therapy, start secondary penicillin prophylaxis every 21 days with benzathine penicillin 1.2 mega units. In penicillin sensitive cases use erythromycin or tetracycline.

Rheumatic Prophylaxis

- **Primordial:** It would be ideal to prevent rheumatic fever by primary (primordial) prophylaxis. In the case of ARF/RHD, primordial prevention means preventing the acquisition of group A streptococcal infection (through implementing actions and measures that target environmental, economic, social and behavioral conditions, cultural patterns of living) and adequate treatment of such infection. In practice, primary prophylaxis focuses on identification and treatment of streptococcal sore throat with penicillin therapy. Beside penicillin therapy, primary prophylaxis requires educating the public on the dangers of streptococcal sore throat infection and need for treatment. Penicillin G, 0.6–1.2 mg units, intramuscularly once daily or oral therapy with penicillin V, erythromycin, amoxicillin, ampicillin, cephalexin, clindamycin or nafcillin for 10 days is necessary. Ten full days therapy is a must, especially when oral drugs are used.
- **Secondary prophylaxis:** It comprises use of the long-acting penicillin, benzathine penicillin, 1.2 mega units once in every 21 days for 27 kg weight and more, and 0.6 mega units for less than 27 kg weight children. Other drugs, which can be used for secondary prophylaxis, include penicillin V, 250 mg twice daily, or erythromycin 250 mg twice daily.

Ideally, the secondary prophylaxis should be continued lifelong. However, some experts recommend it till 40 years of age since risk of recurrence of rheumatic fever after 40 years is negligible. In patients with no residual lesion, one may consider giving secondary prophylaxis for a limited duration. WHO guidelines are summarized in Box 27.12. Appropriate prophylaxis against infective endocarditis is very much essential.

Prognosis

Prognosis depends upon the severity of the disease, especially the carditis. Children with severe carditis are at increased risk of chronic sequelae in the form of rheumatic valvular heart disease. Mortality rate is high in patients who develop CCF. Infective endocarditis can complicate

Box 27.12

World Health Organization guidelines for duration of secondary prophylaxis in rheumatic fever/rheumatic heart disease

- **Rheumatic fever without carditis:** For 5 years after the last attack, or until the age of 18 years (whichever is longer).
- **Rheumatic fever with carditis:** For 10 years after the last attack, or until the age of 25 years (whichever is longer).
- **Rheumatic heart disease (established):** Lifelong.

the course and increase both morbidity and mortality. Patients with mild carditis may improve well. The mitral regurgitation may spontaneously disappear over a period of time (usually 1–2 years). However, aortic regurgitation may not correct spontaneously. Ideal is to prevent occurrence of rheumatic fever with early diagnosis and treatment.

RHEUMATIC HEART DISEASE

The only chronic sequelae of rheumatic fever are rheumatic heart disease. It is the most common acquired heart disease in children. The disease is basically valvular heart disease affecting the heart valves either in isolation or in combination. Mitral valve is the commonly involved followed by aortic valves.

Mitral Regurgitation

Mitral regurgitation is the most common and earliest manifestation of rheumatic carditis. Varying degree of mitral regurgitation occur in almost all cases of acute carditis.

Pathophysiology

The structural changes that occur in the mitral valves are shortening and thickening of the chordae tendineae. The abnormal valves result in regurgitation. Persistent high volume overload results in enlargement of the left ventricle and subsequently left atrium is also enlarged due to regurgitation of the blood. The persistent mitral insufficiency results in elevated pulmonary pressure (pulmonary hypertension), right ventricular enlargement and right heart failure. The mitral regurgitation that occurs during acute rheumatic fever usually subsides by about a year as evidenced by disappearance of mitral regurgitation murmur. Most often the mitral regurgitation is mild to moderate and remains asymptomatic for a longer time.

Clinical Features

Clinical manifestations are dependent on the severity. Patients with mild regurgitation may be symptomatic. Patients with moderate to severe regurgitation develop easy fatigability and dyspnea on exertion. Others include symptoms of CCF, palpitation and weakness.

On examination, heart is enlarged; apex is displaced downwards and outwards with a heaving apical impulse and often with an apical thrill. The first heart sound is normal, second heart sound is accentuated with augmented pulmonary component, a pansystolic murmur is heard at the apex with radiation to the left axilla (Fig. 27.24). Third heart sound may be heard at the apex, indicating increased early rapid filling of the left ventricle. In severe mitral regurgitation, diastolic murmur may be

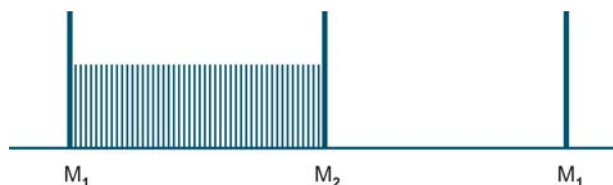


Fig. 27.24: Classical pansystolic murmur of mitral incompetence.

heard at apex due to large blood flow from left atrium to the left ventricle. The diastolic murmur is of shorter duration and ends in mid-diastole. It may be associated with diastolic thrill.

Diagnosis

- **Chest X-ray** shows left ventricular enlargement, left atrial enlargement and features of pulmonary venous hypertension.
- **Electrocardiogram** is normal in mild and asymptomatic cases with normal axis. In moderate to severe cases, ECG shows LVH, left atrial hypertrophy and features of RVH also in severe cases. It may also show arrhythmic changes.
- **Echocardiogram** shows enlarged left atrium and the ventricle.
- **Dopplerecho** shows the severity of mitral regurgitation.

Differential Diagnosis

Beside rheumatic etiology, various other causes of mitral regurgitation in children include septum primum type of ASD, papillary muscle dysfunction, Marfan syndrome, Hurler syndrome, anomalous origin of left coronary artery from pulmonary artery, congenital mitral regurgitation, left ventricular fibroelastosis and septum secundum type of ASD with floppy mitral valve.

Treatment

- Medical management of mitral regurgitation includes treatment of CCF, prophylaxis and treatment of infective endocarditis. CCF requires digoxin and lasix. Afterload reducing agents are useful in the long-term management.
- Surgical treatment is indicated for severe mitral regurgitation resulting in recurrent heart failure, progressive cardiomegaly often with pulmonary hypertension. The surgical measures include prosthetic mitral valve replacement mainly. Annuloplasty has been found to provide good results in older children, though valve replacement may be required later.

Complications

Complications include repeated CCF, infective endocarditis, pulmonary hypertension, arrhythmias, atrial fibrillation, atrial flutter and ventricular extrasystole.

Mitral Stenosis

Rheumatic mitral stenosis is less common in pediatric age group. Unlike mitral regurgitation, mitral stenosis develops late in children. It takes usually more than 10 years to develop following acute rheumatic carditis. However, **juvenile mitral stenosis**, an entity coined to

describe rapid occurrence of mitral stenosis in children, occur rapidly within few years after the carditis. It is more common in children in South Indian, Sri Lanka and some other parts in Asia.

Pathophysiology and Hemodynamics

Mitral stenosis result from fibrosis of the mitral ring, commissural adhesions, contractures of the valve leaflets, chordae tendineae and papillary muscles. The resultant reduction in valvular orifice causes an increased pressure and volume load on the left atrium, resulting in its enlargement. Persistent high pressure leads to pulmonary venous hypertension followed by pulmonary arterial hypertension, right atrial and right ventricular enlargement. This results in right heart failure.

Clinical Features

The development of mitral stenosis usually takes more than 10 years. However, children with juvenile mitral stenosis present early. The symptoms usually start appearing when the orifice size is reduced to 25% or less of the expected normal. Children with mild stenosis are asymptomatic or present with mild symptoms like tiredness and dyspnea. Patients with severe mitral stenosis present with progressive exertional dyspnea or even dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea and palpitation. Hemoptysis can occur due to rupture of bronchial or bronchiolar veins. Blood streaked sputum may be seen in patients who develop pulmonary edema. In patients with chronic severe mitral stenosis, cyanosis and malar flush are noted. Features of CCF can occur in moderate to severe stenosis with pulmonary hypertension. Arrhythmias aggravate the symptoms of mitral stenosis.

Diagnosis

- **Physical examination** shows low volume pulses, distended neck veins, jugular venous pulse show prominent 'a' wave, dominant 'V' wave in the presence of tricuspid regurgitation and systolic pulsation of the liver. Precordium reveals normal sized heart in mild mitral stenosis. But in moderate to severe mitral stenosis, there will be moderate to huge cardiomegaly. Apical impulse is either normal or tapping type. Parasternal right ventricular type of lift may be present with high pulmonary pressure.
- **On auscultation**, first heart sound is loud, an opening snap of mitral valve, best audible just medial to the apex is present. A long, low pitched, rumbling mitral diastolic murmur with presystolic accentuation is heard at the apex. The murmur may be absent in the presence of congestive heart failure. The absence of presystolic accentuation of the murmur is against the diagnosis of mitral stenosis. Second heart sound is loud in the presence of pulmonary hypertension. A pansystolic murmur of low intensity may be heard due to tricuspid regurgitation. Graham Steell murmur (early diastolic murmur) of pulmonary insufficiency may be heard (Fig. 27.25).

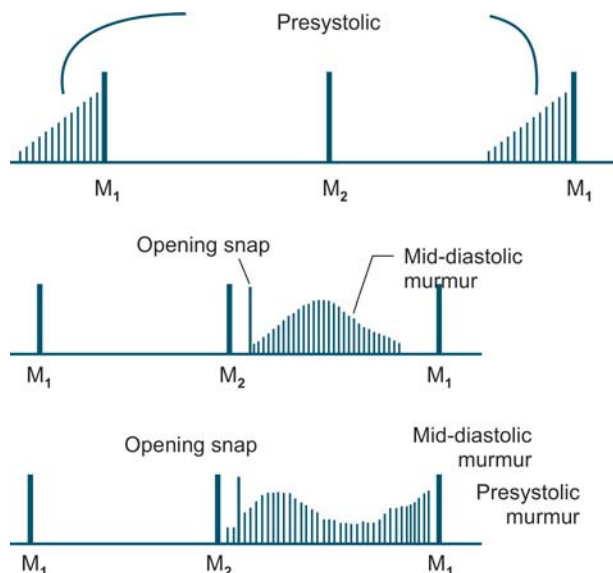


Fig. 27.25: Classical auscultatory findings of mitral stenosis.

- **X-ray of chest** shows enlarged left atrium, right ventricle, plethoric pulmonary field and prominent pulmonary artery. Features of pulmonary edema may be seen.
- **Electrocardiography** shows right axis deviation with RVH and prominent and notched 'P' waves.
- **Echocardiography** show thickened mitral leaflets decreased EF slope, paradoxical posterior leaflet motion, dilation of left atrium, pulmonary artery, right ventricle and right atrium in severe cases. Cardiac catheterization quantifies the diastolic gradient across the mitral valve and the degree of elevated pulmonary pressure.

Management

- Medical management includes restriction of activity, treatment of CCF, prophylaxis against rheumatic recurrence and infective endocarditis.
- Surgical treatment is indicated in subjects with severe mitral stenosis, before the appearance of severe manifestations mentioned earlier.
 - Closed mitral valvotomy is done to relieve the obstruction. It is still the most common and best surgical approach. However, its limitations are that it relieves commissural fusion, but cannot relieve subvalvar fusion and shortening of the chordae tendineae. Hence, it is less useful in patients with more of subvalvar fusion.
 - Balloon valvuloplasty is indicated in symptomatic patients with stenotic, pliable and noncalcified valves without atrial arrhythmias or thrombi.
 - Restenosis may warrant repeat valvotomy. A severely damaged valve may require replacement with prosthetic valve and lifelong anticoagulant therapy.

Aortic Regurgitation

After the mitral valve, the cardiac valve most often involved in rheumatic heart disease is the aortic valves. Rheumatic aortic stenosis does not occur in pediatric patients.

Aortic regurgitation is the most common type of rheumatic valvular disease after the mitral regurgitation in pediatric practice. Isolated aortic regurgitation is rare and occurs in about 5–8% of the patients. On the other hand, combined mitral and aortic regurgitation is common.

Pathophysiology and Hemodynamics

The aortic valvular disease occurs due to sclerosis of aortic valves, leading to shortening, distortion and retraction of the cusps, which causes inadequate closure during diastole. Consequently, hypertrophy of the left ventricle occurs. Regurgitation of the blood through the incompetent aortic valve results in increased left ventricular volume load. The left ventricle accommodates the extra volume by increased ventricular size. The dilatation of the left ventricle is directly proportionate to the degree of aortic leak. The regurgitation of blood results in impaired systemic blood flow (decreased cardiac output). Left ventricle tries to compensate for this decreased output by increased ejection during early part of the systole.

However, the significant aortic regurgitation results in low cardiac output. This result in wide peripheral pulse pressure, and it can be identified as exaggerated arterial and arteriolar pulse pressure. In the initial stages, with the good left ventricular function, even the moderate aortic regurgitation is tolerated. However impaired ventricular function results in increased regurgitation, increased left atrial pressure, which in turn results in pulmonary congestion. Progressive left ventricular dilation results in mitral regurgitation.

Clinical Features

Mild to moderate aortic regurgitation with good ventricular function does not give rise to symptoms. However, persistent and increased regurgitation results in onset of the symptoms. Palpitation is the main symptom of aortic regurgitation. Others include exercise intolerance and exertional dyspnea and paroxysmal dyspnea. Angina may occur later. The signs of wide pulse pressure are evident on the physical examination. The diastolic blood pressure may be even zero. Other peripheral signs of aortic regurgitation have been listed below (Table 27.8).

Table 27.8: Peripheral signs of aortic regurgitation

- **Corrigan's sign:** Prominent carotid pulsations.
- **Corrigan or water hammer pulses:** Sudden falling of the pulse when the limb is elevated from supine position above the level of heart.
- **Musset's sign:** Nodding of the head with each systole.
- **Hill's sign:** Increased difference in blood pressure between brachial and femoral arteries. (Difference of <20 mmHg—normal, 20–40 mmHg—mild aortic regurgitation, 40–60 mmHg—moderate, >60 mmHg severe aortic regurgitation).
- **Pistol shot sounds:** Sounds resembling pistol shot heard over the brachial or femoral artery without pressure.
- **Duroziez's sign:** A combination of systolic and diastolic murmurs heard over the brachial or femoral artery on applying pressure on the artery. Application of pressure proximally produces systolic murmur and pressure distal to the chest piece produces a diastolic murmur. Pulsations may be seen over the uvula, tip of the tongue, ear lobule and pupils.

Precordial examination shows left ventricular type of cardiac enlargement with heaving apical impulse and seesaw movements of the chest in severe cases. The first heart sound is soft and aortic component of second sound is either audible or masked by the murmur. A diastolic thrill may be felt. The typical aortic regurgitation murmur is a diastolic murmur, begins immediately after the second heart sound and continues until the late diastole. It is a hollow, high-pitched blowing quality murmur, best heard along left upper and mid-sternal border with radiation to the apex and aortic area. The murmur is better appreciated with the diaphragm of the stethoscope firmly placed over the chest with patient leaning forward. An ejection systolic murmur, with preceding click may be heard due to large stroke volume. An apical presystolic murmur (Austin flint murmur) of mitral origin may be heard.

Diagnosis

- **X-ray of chest** shows enlargement of the left ventricle and dilatation of the aorta.
- **Electrocardiogram** may be normal in mild cases and shows evidence of LVH with strain pattern in severe cases.
- **ECG** shows large left ventricle, dilated aorta and diastolic mitral valve flutter caused by regurgitant flow hitting the valve leaflets.
- **Doppler study** demonstrates the severity of aortic regurgitation.

Treatment

- The medical management consists of prophylaxis against rheumatic recurrence and infective endocarditis. For patients who develop congestive heart failure, vasodilators, mainly the angiotensin-converting enzyme inhibitors are useful. Use of digoxin increases the regurgitation and generally not recommended.
- Ideally, the surgery should be done before the patient develop signs of left ventricular failure, angina or pulmonary edema. The surgery consists of aortic valve replacement by homograft or a prosthetic valve.

Prognosis

Mild to moderate degrees of aortic regurgitation are well tolerated. Some patients may remain asymptomatic almost into the third and fourth decade.

Tricuspid Regurgitation

The tricuspid valve involvement is rare following rheumatic fever. Tricuspid disease occurs either alone or in combination with other valvular diseases. Isolated tricuspid regurgitation is rare. Most often, it is seen in association with other valvular heart disease mainly mitral valve (mitral stenosis and mitral regurgitation) and most often it is a functional regurgitation. Organic tricuspid regurgitation can occur with mitral regurgitation.

Hemodynamics

Tricuspid regurgitation results in right atrial volume overload and consequent right atrial enlargement. Regurgitation of blood into the right ventricle results in right ventricular enlargement and pulmonary hypertension.

Clinical Features

There is no specific symptomatology due to tricuspid regurgitation. Occasionally patient may complain of right hypochondrial pain due to congested liver. The signs include 'V' waves on the jugular venous pulse, systolic pulsation of the liver and blowing holosystolic murmur, best heard along the left lower sternal border. Signs of pulmonary hypertension may be present along with the features of mitral valvular lesion.

Diagnosis

- **Electrocardiogram** shows right ventricular and right atrial hypertrophy.
- **Echocardiogram and doppler** confirms the diagnosis and also document the severity of regurgitation.

Treatment

Irrespective of whether the tricuspid regurgitation is organic or functional, decongestive measures should be undertaken. This result in reduction in the regurgitation of the tricuspid regurgitation. If the tricuspid regurgitation is due to mitral valve disease, the corrective measures result in decrease or disappearance of tricuspid regurgitation. Rarely tricuspid regurgitation requires tricuspid valvuloplasty.

ENDOMYOCARDIAL DISEASES

These are the group of disorders that involve the endocardium or myocardium regardless whether the cause is known or unknown. Features common to these diseases are cardiac enlargement, CCF and arrhythmias. The diseases falling under this heading are:

- Endocardial fibroelastosis
- Endocardial fibrosis
- Cardiomyopathy
- Myocarditis.

Endocardial Fibroelastosis

It is a relatively common cause of CCF in infancy. It is characterized by thickening of the endocardium of left ventricle in particular. Mitral incompetence is frequently associated.

- **Chest X-ray** shows cardiomegaly involving mainly the left ventricle and atrium.
- **Electrocardiography** shows cardiomegaly involving mainly the left ventricle and atrium, conduction disturbances and arrhythmias.

Systemic embolization may follow mural thrombi which are quite common in this disease. Therapy is directed at controlling the CCF. Prognosis is bad.

Endomyocardial Fibrosis

It is characterized by occurrence of fibrosis in the inflow tract and the apex of one or both ventricles. The signs and symptoms depend on whether the right side chambers or left side chambers of the heart are involved.

- **Chest X-ray** shows cardiomegaly; intramyocardial calcium deposits may be visualized.
- **Electrocardiography** usually shows low voltage. Cardiomyopathy in which myocardium is involved, but there is no structural cardiac deformity.

492 CARDIOMYOPATHY

Definition

The term denotes a disease entity in which the presenting manifestations result exclusively or predominantly from dysfunction of the myocardium without any structural deformity of the heart. It may be:

- **Primary:** No cause is known
- **Secondary:** The dysfunction is secondary to generalized diseases such as hypertension, amyloidosis, hemochromatosis, SLE, leukemia, muscular dystrophy, glycogenosis or gargoylism.

However, by convention, use of the term **cardiomyopathy** is restricted to primary myocardial involvement without any known cause.

Clinical Categories of Primary Cardiomyopathy

- **Dilated (congestive)**, characterized by CCF, arrhythmias, murmurs of mitral and tricuspid incompetence and emboli. It is most common type in childhood.
- **Restrictive**, characterized by restriction to ventricular filling.
- **Hypertrophic** may be with or without obstruction to ventricular outflow. As given category may present some features of others, either at the same time or after a course of time.

Dilated (Congestive) Cardiomyopathy

The most frequently encountered myopathy of childhood may have acute or subacute onset with vulnerability to thromboembolic phenomenon. Murmurs of mitral regurgitation and, sometime, tricuspid incompetence are present.

- **Chest X-ray** shows enlarged heart without any evidence of structural abnormality (Fig. 27.26).
- **Electrocardiography** shows nonspecific changes in ST and T, often with LVH. Arrhythmias may be present.
- **Echocardiography** shows dilatation of ventricular cavity but without hypertrophy of the ventricular wall



Fig. 27.26: Dilated cardiomyopathy. Note the enlarged cardiac shadow without any structural cardiac lesion. This is the most common cardiomyopathy encountered in children.

or septum, and remarkable reduction in left ventricular contractility.

- **Myocardial biopsy** is indicated in subjects who are refractory to standard treatment.
- **Differential diagnosis** from anomalous left coronary artery from pulmonary artery (ALCAPA).
- Treatment comprises of:
 - Bed rest
 - Anticongestive therapy—ACE inhibitors
 - Intermittent dopamine infusions
 - Beta blockers—Metoprolol, carvedilol
 - Carnitine.

Restrictive Cardiomyopathy

The patient with restrictive cardiomyopathy is generally in CCF with dependent edema, ascites and an enlarged, tender liver. The jugular venous pressure is persistently elevated. Cardiomegaly is invariably present. The heart sounds are distant. Usually, third and fourth heart sounds are audible. Murmurs are, as a rule, not distinctive.

- **Chest X-ray** shows cardiomegaly without any calcification in the region of pericardium.
- **Electrocardiography** shows low voltage. Arrhythmias and ST-T wave changes are common.

This kind of cardiomyopathy is difficult to be differentiated from constrictive pericarditis even with the aid of cardiac catheterization.

Hypertrophic Cardiomyopathy

The idiopathic hypertrophic subaortic stenosis (IHSS) is characterized by enormous hypertrophy of the left ventricle, most remarkably in the interventricular septum.

What is striking in IHSS is that the obstruction to outflow is dynamic, changing every few minutes. This is in marked contrast to the fixed narrow orifice in the case of valvular aortic stenosis. The disease is familial in 33% of the cases, though most often it does not manifest at birth or early in life.

INFECTIVE ENDOCARDITIS

Infective endocarditis refers to the infection of endocardium of the heart including endocardium of the valves, mural endocardium or endothelium of the blood vessels. Previously it was called bacterial endocarditis. However as many other organisms other than bacteria also cause endocarditis; it has been labeled as infective endocarditis. It has significant mortality and also significantly influences the prognosis of underlying heart disease. It is a major complication of underlying heart disease.

Etiology

Streptococcus viridans was the most common cause. However, of late, *Staphylococcus* has become increasingly more common and currently it is responsible for a large number of cases. It is also a common cause in patients who do not have underlying heart disease. Other less common causes include *Streptococcus pneumoniae*, *Hemophilus* species, *Staphylococcus epidermidis*, *Coxiella burnetii*, chlamydial species, *Neisseria gonorrhea*, fungus, rickettsiae and others.

Infective endocarditis predominantly occurs in patients with underlying heart disease: congenital or acquired. Rarely does it occur in normal heart, usually as a part of septicemia. Various risk factors for the occurrence of infective endocarditis include presence of an underlying heart disease, drug abuse, prosthetic heart valves, recent cardiac surgery, and various interventions like dental procedures, cardiac catheterization, genitourinary procedures and infective process anywhere in the body.

Pathogenesis and Pathology

Pathogenesis generally depends on the virulence of the organism. Infective endocarditis usually starts in places where there is high velocity of blood ejection (through a hole or stenotic orifice like VSD and aortic stenosis). The vegetation usually formed at the site of endocardial or intimal erosion that result from the turbulent blood flow. The bacteremia resulting from infection elsewhere in the body result in deposition of the bacteria on the endocardium and initiates the endocarditis. Endocarditis also results in immune-mediated vasculitis and thrombocytopenia.

Clinical Features

Clinical features depend on the virulence of the organism and the severity of the disease. Depending upon the course, it can be either acute or subacute. Prolonged fever, without any other manifestation, in patients with underlying heart disease may be the only clinical feature. Alternatively patient may present with high spiking fever, chills and rigors, night sweat and prostration. In most cases, however the presentation is in between these two. Patients present with persistent fever, with or without chills/rigors, generalized malaise, loss of appetite, loss of weight, myalgia, arthralgia, headache, nausea and vomiting. Patients may also develop CCF. New murmur or changing murmurs can occur, and they are the important findings that give clues to the diagnosis while evaluating the patients. Splenomegaly is a relatively common feature. Various thromboembolic complications include mainly central nervous system complications—brain abscess, embolism, mycotic aneurysms and hemorrhages, pulmonary and other systemic and peripheral embolus phenomenon resulting in renal infarct, systemic infarct and mesenteric embolisms. Myocardial abscesses and pericardial involvement can also occur, especially with *Staphylococcus aureus* infection. Features of immunological response presenting as vasculitis are Osler nodes (tender pea-sized intradermal nodules in the pads of fingers and toes), Janeway lesions (painless erythematous or hemorrhagic lesions on palms and soles), splinter hemorrhages below the nail bed, petechiae over the skin, mucous membranes and retina (Roth's spot).

Investigation

- **Blood culture** is the gold standard in the diagnosis of infective endocarditis. All other tests are complementary. Three to five samples collected separately from aseptically prepared sites can find positive growth in

more than 95% of cases. As bacteremia is expected to be constant, timing of the sampling is not important. Anaerobic culturing is also necessary in all cases. In our country, unfortunately nearly 50% samples are negative. The major reason for negative blood culture is prior antibiotic therapy. Others include slow growing organisms, fungus, atypical and anaerobic organisms. The blood culture also helps in finding sensitivity pattern and helps in meticulous use of antibiotics.

- **Other laboratory abnormalities** include anemia, leukocytosis, raised ESR, C-reactive protein, microscopic hematuria, hypergammaglobulinemia, hypocomplementemia, cryoglobulinemia and positive rheumatoid factor.
- **Echocardiogram** is another important diagnostic tool, especially when the blood culture is negative. The presence of vegetations is suggestive of infective endocarditis. It is very sensitive in identifying vegetations on mitral and aortic valves. It can identify vegetations measuring more than 2 mm size. Vegetations may not be visible in the early stage of the disease.

Complications

Patients with severe endocarditis can have many complications like perforation of the valve, rupture of chordae tendineae, acute valvular regurgitation due to any of the above complications, thromboembolic phenomenon with systemic involvement, mycotic aneurysms and others.

Diagnosis

High index of suspicion in patients with underlying cardiac disease is important to make the diagnosis of infective endocarditis. Blood culture is the gold standard. However as discussed above, echocardiography has an important role, especially in cases of culture negative cases. Other investigations are complimentary to the blood culture.

Treatment

It is a medical emergency. Patients require admission into the hospital and require prolonged antibiotic therapy and good supportive therapy. Delayed diagnosis and late initiation of treatment are the main reasons for complications and high mortality.

Antibiotics should be administered in higher doses (5–20 times the minimum *in vitro* inhibiting concentration) to destroy the growing organisms in the vegetations. Minimum of 4–6 weeks of antibiotics are required. Depending upon the clinical response, laboratory response and echocardiograph evaluation, further continuation of the antibiotics should be decided. Before the availability of blood culture report and in blood culture negative cases, start broad-spectrum antibiotics to cover wide range of organisms.

Start with high dose of ampicillin and an aminoglycoside. Once blood culture report is available, choice of antibiotics should be as per the sensitivity pattern. Table 27.9 lists the antibiotics used in the treatment of infective endocarditis.

Table 27.9: Dosages of the drugs used in the treatment of infective endocarditis

Penicillin G	200,000–300,000 units/kg/day, 4–6 hourly
Gentamicin	7.5 mg/kg/day, 8–12 hourly
Amikacin	15–25 mg/kg/day, 8–12 hourly
Vancomycin	60 mg/kg/day, 8–12 hourly
Cloxacillin	150–200 mg/kg/day, 4–6 hourly

For *Streptococcus viridans* use penicillin G alone or penicillin G and an aminoglycoside (gentamicin or amikacin). For *Enterococcus* species use penicillin G or ampicillin with gentamicin or amikacin. For *Staphylococcus aureus*, if methicillin sensitive, use cloxacillin and gentamicin/amikacin. If methicillin resistant, use vancomycin and gentamicin/amikacin. In severe cases, rifampicin may be used as an additional optional drug. Duration of therapy for *Staphylococcus aureus* endocarditis ranges from 6 weeks to 8 weeks.

In culture negative endocarditis, use cloxacillin with gentamicin for 4–6 weeks. Use ampicillin as an optional drug. For fungal endocarditis the drugs used are amphotericin and flucytosine. The dose of amphotericin is 1.0 mg/kg/day. Start with 0.25 mg/kg/day and gradually increase. The maximum dose is 1.5 mg/kg/day. 5-flucytosine 5–150 mg/kg/day, every 6 hour orally. Surgery may be required to remove the vegetations. However, the success rate for surgical treatment is limited. It is more difficult to treat endocarditis in patients with prosthetic valves. In these patients, beside antibiotic therapy, prophylactic valve replacement may be necessary. Oral anticoagulants, instead of heparin should be used.

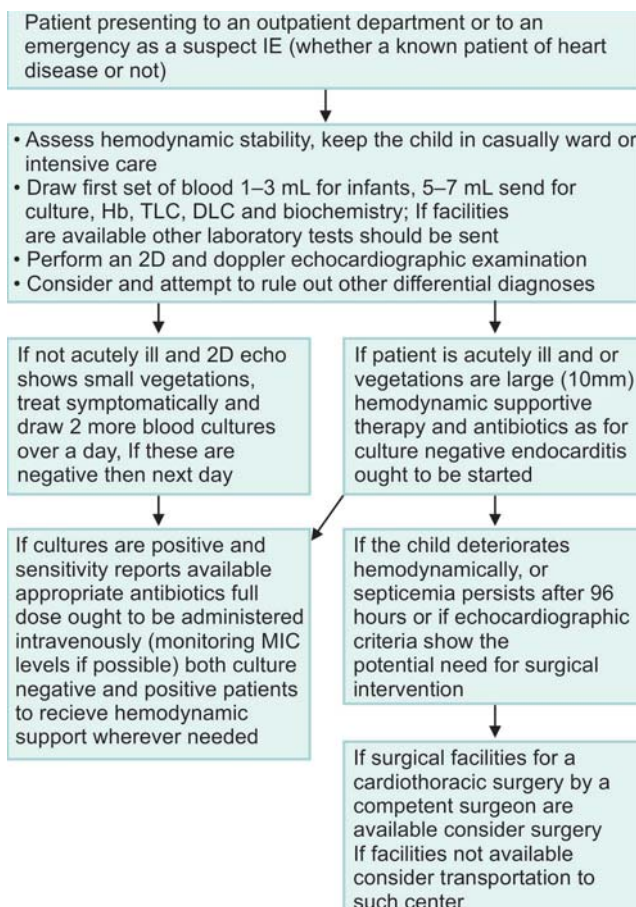
Surgical treatment may be required in some cases, and it is an integral part in the treatment of infective endocarditis. Surgical interventions are required for mitral or aortic regurgitation leading to severe CCF, mycotic aneurysms, rupture of an aortic sinus, dehiscence of intracardiac patch. Other causes include failure to sterilize blood despite adequate antibiotic therapy, myocardial abscess and recurrent emboli. Other supportive measures include bed rest, nutritious diet, if present, treatment of congestive failure, monitoring and treatment of arrhythmias and any other coexisting problems. Fig. 27.27 presents an algorithmic approach to management of pediatric IE.

Prognosis

The survival has significantly improved with the availability of potent antibiotics. However, in spite of adequate antibiotic therapy, the mortality rate remains at 20–25%. Delayed diagnosis and late initiation of therapy may become life threatening.

Prophylaxis and Prevention

The best method to prevent infective endocarditis is early appropriate surgical treatment of the underlying heart disease. However, as it is not always possible, prophylactic antibiotic therapy should help in reducing the incidence of infective endocarditis in susceptible patients. Proper

**Fig. 27.27:** Algorithmic approach to management of pediatric IE.

Abbreviations: Hb, hemoglobin; TLC, total leukocyte count; DLC, differential leukocyte count; IE, infective endocarditis; MIC, minimum inhibitory concentration.

hygiene and treatment of other foci of infections are also important. Recommended antibiotics for various procedures are as follows:

- **Dental procedures and upper respiratory tract surgeries:** Amoxicillin (O): 50 mg/kg 1 hour prior to surgery, 25 mg/kg after the initial dose; erythromycin (O): 20 mg/kg 2 hour before the procedure and 10 mg/kg 6 hour after the initial dose or clindamycin: 10 mg/kg 1 hour before surgery and 5 mg/kg 6 hour after the initial dose.
- **Gastrointestinal and genitourinary tract surgery:** Ampicillin (IV/IM): 150 mg/kg and gentamicin 2 mg/kg 30 minutes before the procedure. In high-risk patients, repeat dose is required 6–8 hours after the procedure. For minor procedures, amoxicillin may be used. In penicillin allergy patients, parental vancomycin 20 mg/kg as infusion 1 hour prior to the procedure along with gentamicin should be given. For high-risk patients, vancomycin dose may be repeated 8 hours after the initial dose.

High-risk patients include patients with prosthetic valves, previous endocarditis, and penicillin prophylaxis for rheumatic fever, surgically constructed systemic pulmonary shunts or conduits (Fig. 27.28).

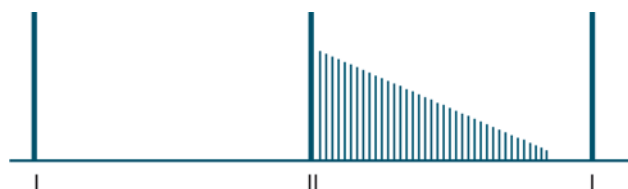


Fig. 27.28: Classical diastolic murmur of aortic incompetence.

PERICARDITIS

Definition

The term **pericarditis** denotes inflammatory or noninflammatory involvement of the pericardium, leading to accumulation of varying amounts and nature of fluid in the pericardial cavity.

As much as 1,000 mL of fluid (serous, purulent or hemorrhagic) may collect in the sac against the normal of 10–15 mL. With rapid rise in amount of fluid and pressure, there may result cardiac compression (cardiac tamponade). The compromised cardiac output may cause shock.

Etiology

Table 27.10 lists the causes of pericarditis.

Clinical Features

- These include precordial pain (presumably referred from pleural and diaphragmatic irritation), cough,

Table 27.10: Causes of pericarditis

Bacterial

- Purulent (pneumonia, osteomyelitis, meningitis, epiglottitis)
- Tuberculous

Viral

- Coxsackievirus B
- Echovirus
- Epstein-Barr virus
- Influenza
- Adenovirus

Fungal

- Histoplasmosis
- Actinomycosis

Parasitic

- Entamoeba histolytica*
- Toxoplasma gondii*

Collagen disorders

- Rheumatic fever
- Rheumatoid arthritis
- Systemic lupus erythematosus

Neoplastic disease

- Primary and metastatic malignancy

Hematologic disorders

- Thalassemia
- Leukemias

Metabolic/Endocrinal

- Uremia
- Hypothyroidism

Miscellaneous

- Radiation injury
- Trauma
- Chronic constrictive pericarditis.

fever and dyspnea on top of manifestations of the primary disease, say malnutrition in tuberculosis, joint pains/swelling in rheumatic fever or rheumatoid arthritis, URI in viral etiology, or significant anemia, generalized lymphadenopathy and bleeding in leukemias, etc.

- Physical examination reveals increased cardiac dullness, a quiet heart, distant heart sounds, pericardial friction rub (only when effusion is reduced), distended neck veins, pulsus paradoxus* (10–20 mm inspiratory drop; over 20 mmHg drop confirms presence of tamponade)
- Onset of constrictive pericarditis is usually insidious and is marked by development of massive hepatomegaly and ascites (suggesting chronic liver disease), distention of neck veins, and pulsus paradoxus.
- In well-established constrictive pericarditis, an early pericardial knock is an important finding.

Diagnosis

- Chest X-ray** shows cardiomegaly with the so-called **water-bottle** configuration in which blunting of the cardiophrenic angles is characteristic (Fig. 27.29). Detection of calcification points to constrictive pericarditis.
- Electrocardiography** findings include low voltage of the QRS complexes, mild elevation of ST segment, and generalized T wave inversion, on top of the findings of the underlying disease.
- Echocardiography** is helpful for assessing the size and progression of effusion.
- Pericardial puncture or tap (pericardiocentesis)**, described elsewhere See Chapter 49 (Pediatric Practical Procedures), is of help in confirming the presence of effusion and whether it is serous, purulent or hemorrhagic.

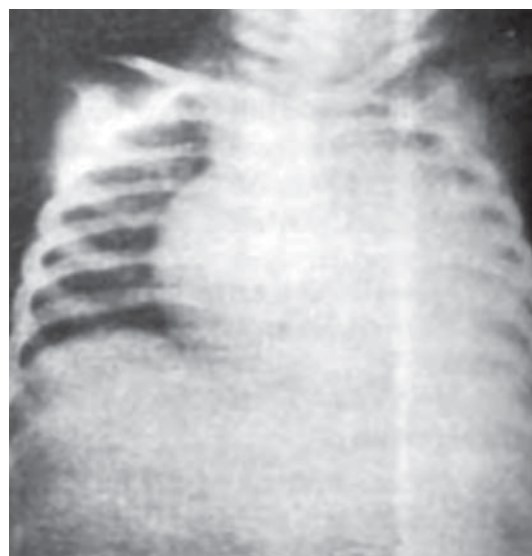


Fig. 27.29: Pericardial effusion. Note the cardiomegaly with blunting of the cardiophrenic angle and the so-called 'water-bottle' configuration.

* Remaining causes of pulsus paradoxus are conditions with gross dyspnea, say bronchial asthma, emphysema, etc., cardiomyopathy (muffling), and post thoracotomy state.

496 Treatment

- Specific measures, including chemotherapy, depend on the etiologic diagnosis.
- Steroids are indicated in pericarditis accompanying rheumatic fever, tuberculosis and collagenosis.
- Aspiration of pericardial effusion in case of pericardial tamponade (upto 200 mL at a sitting), under monitoring by ECG, can be lifesaving.
- Other measures include bed rest, oxygen inhalation, antipyretics, correction of anemia and maintenance of fluid and electrolyte balance as well as nutrition.
- Decongestive therapy with digoxin for CCF accompanying pericarditis is best avoided.
- Surgical intervention (radical pericardiectomy with decortication of pericardium) leads to gratifying response in constrictive pericarditis.

DEXTROCARDIA

The term refers to the presence of the heart in the right hemithorax with its apex pointing to the right.

Dextrocardia with Situs Inversus (Fig. 27.30)

This is the most common type. Here the position of the thoracic and abdominal viscera is also reversed. Since there is transposition of all the organs to opposite side, cardiac hemodynamics remain normal. In an individual with this condition, the physician can find the normal liver on left side. Incidence of cardiac defects is low.

Association of situs inversus with chronic bronchitis (sometimes with bronchiectasis) and chronic sinusitis (usually with otitis media) is termed as **Kartagener syndrome**, immotile cilia syndrome or dyskinetic cilia syndrome. Differential diagnosis is from conditions that push or pull the heart to the right hemithorax.

To confirm diagnosis, screening and X-ray chest are of value. Barium meal studies reveal a gastric gas bubble on the right, confirming that the stomach is under the right diaphragm. ECG shows that, in lead I, P and T waves are inverted; in a VR, these waves are upright.

Isolated Dextrocardia (Without Situs Inversus)

This is a serious condition, nearly always killing the patient in infancy or preschool years. The bad prognosis is chiefly due to the associated CHD. Tricuspid atresia, single ventricle,



Fig. 27.30: Dextrocardia with situs inversus.

transposition of the great vessels and TOF rank prominently among the congenital cardiac associations reported so far.

Levocardia with Situs Inversus

This is another serious condition that usually kills the patient during early years. Here, position of the heart is normal. The abdominal organs are, however, on the opposite side, totally or partially.

A variety of splenic anomalies have been described in association with levocardia. These include absence of spleen (asplenia) or rudimentary spleen. The presence of precipitated hemoglobin (Heinz bodies) or nuclear remnants (Howell-Jolly bodies) in the RBC should arouse suspicion of splenic abnormality.

The various cardiac defects reported are—single ventricle, atrioventricular canal, pulmonary stenosis, transposition of the great vessels and anomalous systemic and pulmonary venous return.

MYOCARDITIS

Myocarditis is an inflammation of the myocardium, usually viral, resulting in mild disease which resolves without any significant treatment or a serious disease with chest pain, CCF, arrhythmias and cardiovascular collapse which can be fatal.

Etiology

A large number of conditions (Table 27.11) may be responsible for myocardial damage in the form of myocarditis. Viral myocarditis is, however, considered to be the most common. The causative agents include Coxsackie virus A and B (predominantly B), Echo, rubella, varicella (herpes) and influenza infections.

Clinical Features

- Early infancy, including neonatal period, is most susceptible to myocarditis.
- Onset of symptoms is usually abrupt, especially in the neonates, with unexplained dyspnea, cardiovascular collapse and CCF.
- In older children, onset is usually gradual with chest pain CCF, which may, at times, become chronic.
- Arrhythmias and conduction disturbances are frequent.

Diagnosis

- **Chest X-ray** shows cardiomegaly with pulmonary venous hypertension.
- **Electrocardiography** shows low voltage and nonspecific ST-T abnormalities.

Treatment

Treatment consists in giving rest and digoxin (only half to 3/4th of standard dose) and ACE inhibitors. Steroids are usually recommended, especially when cardiovascular collapse and conduction disturbances are present, provided that acute viremia phase is over.

Table 27.11: Causes of myocarditis

Viral infections	Metabolic and nutritional diseases
<ul style="list-style-type: none"> • Coxsackie virus A and B • Rubella • Varicella, influenza 	<ul style="list-style-type: none"> • Beriberi • Iron deficiency • Kwashiorkor
Bacterial Infections	Neuromuscular diseases
<ul style="list-style-type: none"> • Diphtheria • Enteric fever dystrophy 	<ul style="list-style-type: none"> • Friedreich ataxia • Progressive muscular
Parasitic infections	Blood disorders
<ul style="list-style-type: none"> • Toxoplasmosis trichinosis • Hydatid disease • Schistosomiasis • Trypanosomiasis (Chaga's disease) 	<ul style="list-style-type: none"> • Anemia from any cause • Inborn errors of metabolism • Glycogen storage disease • (Type 2 or Pompe disease) Gorgoylism
Coronary arteries damage	Fungal infections
<ul style="list-style-type: none"> • Histoplasmosis • Coccidiomycosis • Actinomycosis • Rickettsial Infections • Rocky Mountain spotted fever 	<ul style="list-style-type: none"> • Kawasaki disease
Mesenchymal disease	Cardiotoxicity
<ul style="list-style-type: none"> • Rheumatic carditis • Rheumatoid arthritis • SLE • Periarthritis nodosa • Dermatomyositis • Scleroderma 	<ul style="list-style-type: none"> • Adriamycin • Cyclophosphamide • Chloroquine • Iron overload • Chloramphenicol • Alcohol • Irradiation • Ipecac

CARDIAC ARRHYTHMIAS (Dysrhythmias)

Cardiac arrhythmias are disorders of abnormal heart rhythm. These are infrequent in pediatric practice. However, *sinus arrhythmia* is a common finding in childhood. In this condition, the heart rate increases with inspiration and decreases with expiration. ECG shows a recurring pattern.

Etiology

Etiology includes infections, drugs, metabolic and endocrine abnormalities, structural lesions and intrinsic conduction defects (Table 27.12).

Types

- Atrial arrhythmias include:
 - Wandering atrial pacemaker
 - Premature atrial contractions
 - Atrial flutter/fibrillation
 - Supraventricular tachycardia
- Ventricular arrhythmias include:
 - Premature ventricular contractions
 - Ventricular tachycardia
- Heart block may be:
 - First degree
 - Second degree
 - Third degree.

Table 27.12: Etiology of pediatric arrhythmias

- **Infections:** Infective endocarditis, myocarditis, rheumatic fever, diphtheria, Guillain-Barré syndrome.
- **Drugs:** Quinidine, caffeine, theophylline, ephedrine, cocaine, tricyclic antidepressants.
- **Metabolic abnormalities:** Dyselectrolytemia (potassium, calcium, magnesium), uremia, porphyria, mitochondrial myopathies, cardiomyopathy.
- **Endocrine:** Thyrotoxicosis, pheochromocytoma.
- **Structural defects:** Congenital heart disease, ventriculotomy, ventricular tumors.
- **Miscellaneous:** Central venous catheter-related, maternal SLE, adrenergic-induced, prolonged QT interval.

Congenital complete heart block is associated with such maternal collagenosis as SLE and Sjögren's syndrome, and CHD. Acquired complete heart block is most often post-surgery. Infections/inflammations and drugs too can cause it.

Supraventricular Tachycardia (Paroxysmal Atrial Tachycardia)

Supraventricular tachycardia, the most common among the tachyarrhythmia, is characterized by paroxysms of very rapid heart rate, varying from 180 to 300 per minute or even more.

Etiology

The underlying cause is re-entry within the A-V node. A premature atrial beat is conducted with delay through the node, initiating tachycardia. The paroxysm may be precipitated by an acute infection or nervous or physical factors. Occasionally, it may accompany a congenital heart lesion.

Clinical Features

These vary with the age of the child.

- **Older children:** Paroxysm has an abrupt onset, usually lasting a few hours with a variation of a few seconds to several weeks. Usually, there is no complaint, except awareness of rapid heart rate. Very rapid and very prolonged attacks may be accompanied by precordial pain and CCF.
- **Infants:** Tachycardia that persists during sleep and quiet periods plus signs of CCF sooner or later are the common manifestations. A paroxysm lasting for more than 6–24 hours, in addition, may be accompanied by slight cyanosis, restlessness, irritability and moribund condition. If PAT occurs during intrauterine life, hydrops fetalis may result.

Diagnosis

An ECG must be done to confirm the diagnosis. The findings include rapid rate, abnormal P waves and a normal QRS complex.

498 In 10% of the PAT cases, ECG may show a short P-R interval and slow upstroke (prolongation) of QRS complex, the delta wave. This is what is called **Wolff-Parkinson-White** (WPW) syndrome. Also called **pre-excitation syndrome**, its presence is an indication for excluding such underlying anomalies as cardiomyopathy, corrected TGV and Ebstein anomaly. Undoubtedly, it may be present in an otherwise normal heart.

Treatment

Subjects in whom PAT does not spontaneously regress may respond to vagal stimulation by a simple procedure like unilateral carotid sinus massage, straining, breath holding, drinking ice water, Valsalva maneuver or adopting a particular position. In an emergency situation, electrical cardioversion may be resorted to.

Drug therapy includes digoxin in digitalizing dose, diphenylhydantoin, quinidine sulfate, propranolol, phenylephrine, edrophonium, calcium channel blockers (verapamil, diazepam). In case of PAT in infants, therapy needs to be maintained for 3–6 months even if a particular paroxysm has been controlled by vagal stimulation.

Sick Sinus Syndrome

Abnormalities in the sinus node and/or atrial conduction pathways, most commonly encountered following operative correction of CHD (particularly the Mustard operation for TGV), result in what is termed as **sick sinus syndrome**.

Clinical Features

Manifestations are variable. Most patients are symptom free. In symptomatic subjects, manifestations include dizziness, syncope (during spans of marked sinus slowing) and supraventricular tachycardia alternating with bradycardia (bradycardia-tachycardia syndrome), leading to palpitations, exercise intolerance or dizziness.

Treatment

Drug therapy is aimed at controlling tachyarrhythmia. This therapy with agents, such as digoxin, propranolol, quinidine, or procainamide may be accompanied by symptomatic bradycardia. A demand for ventricular pacemaker is, therefore, mandatory along with drugs in the symptomatic subjects with sick sinus syndrome.

Long QT Syndrome

This rare syndrome is characterized by prolonged QT interval, syncopal attacks and a variety of neurologic manifestations including nerve deafness, left-sided hemiplegia, absence spells and seizure-like episodes. SIDS may occur. The fundamental defect appears to be an imbalance in sympathetic innervation of the ventricular myocardium which predisposes it to paroxysmal ventricular tachycardia and fibrillation. Two forms of the syndrome are recognized:

- **Congenital**, which may be autosomal recessive as in Jervell and Lange-Nielsen syndrome, or autosomal dominant as in Romano-Ward syndrome.

- **Acquired**, which may be secondary to:

- **Drugs:** Quinidine, procainamide, phenothiazines, tricyclic antidepressants.
- **Electrolyte imbalance:** Hypokalemia, hypomagnesemia, hypocalcemia
- Hypothermia
- Cerebrovascular disease
- Neck surgery.

Therapeutic measures include propranolol, diphenylhydantoin and left stellate ganglionectomy. Mortality in untreated cases is very high—around 73%. With timely treatment, it is only 6%.

SYSTEMIC HYPERTENSION

Hypertension is defined as the blood pressure of 95th percentile or more with reference to the age and sex (Box 27.5). Normal blood pressure in children is related to the age and sex and, hence, one has to refer to the nomograms charts for normal blood pressure values (Table 27.13). Blood pressure measurement up to 90th percentile is considered normal, though one has to watch for hypertension when the blood pressure is persistently about 90th percentile. Between 90th and 95th percentiles, it is labeled as **prehypertension** or **borderline** high blood pressure.

Blood Pressure Measurement in Children

An accurate measurement of blood pressure is important, and it requires due attention to the comfort of the child, proper skills and techniques of blood pressure measurement. For correct measurement of blood pressure, selection of appropriate sized cuffs is important in children. The age-appropriate cuff sizes are: infants—2.5 cm; 1–12 months—5 cm; 1–8 years—9 cm; and older children—12.5 cm. Systolic pressure is indicated by appearance of Korotkoff sound and the diastolic pressure is ideally noted when the sounds are muffled. However, if it is not possible to appreciate the change in the intensity of the sounds, disappearance of the sounds may be recorded as diastolic blood pressure. In children, blood pressure is measured by palpatory method (the appearance of radial pulsation while deflating the cuff is systolic blood pressure) and auscultatory method. In infants, the methods are flush method, oscillometry and Doppler methods.

Box 27.13

Important definitions and staging of pediatric hypertension

- **Hypertension:** Average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) >95th percentile for age, sex and height on at least 3 occasions.
- **Prehypertension:** SBP or DBP between 90th percentile and 95th percentile.
- **Stage 1 hypertension:** 95th–99th percentile +5 mmHg.
- **Stage 2 hypertension:** 95th percentile +5 mmHg.

Source: National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. Pediatrics. 2004;114 (2 Suppl 4th Report):555–576.

Table 27.13: Normal blood pressure (mmHg)

Age	Mean + 2 SD	Systolic	Mean + 2 SD	Diastolic
1 month	80 +	16	46 +	16
6–12 months	89 +	29	60 +	10
1 year	96 +	30	66 +	25
2 years	99 +	25	64 +	25
3 years	100 +	25	67 +	23
4 years	99 +	20	65 +	20
5–6 years	94 +	14	55 +	9
6–7 years	100 +	15	58 +	8
7–8 years	102 +	15	56 +	8
8–9 years	105 +	16	57 +	9
9–10 years	107 +	16	57 +	9
10–11 years	111 +	17	58 +	10
11–12 years	113 +	18	59 +	10
12–13 years	115 +	19	59 +	10
13–14 years	118 +	19	60 +	10

Box 27.14**Flush method of recording blood pressure in infants**

- To start with, the infant must be quiet and comfortable. You may give him a pacifier or a feeder.
- Then the cuff (2.5–3 cm size so that it covers the 2/3rd of the limb) is applied. It is, however, not inflated. An elastic crepe bandage or a rubber band, about 2.5 cm wide, is applied round the forearm distal to the cuff.
- The cuff is inflated to around 200 mmHg. At this stage, the crepe bandage or band is speedily removed. As the cuff is gradually deflated, a flush appears in the forearm. At this point, the pressure is noted. This is the mean blood pressure of the infant.

Caution: For the next 15 minutes, the method must not be repeated.

Box 27.14 shows procedure of flush method of blood pressure recording in infants. Electronic transducer (ultrasound) and oscillometry are far more sophisticated methods of recording blood pressure in infants.

Etiology

In children, the hypertension is due to secondary causes in over 90% of the case. Among them renal, causes account for about 75% of cases. The essential hypertension, hypertension without any known underlying disease, accounts for only 5–10% of cases in children. However, these patients have family history, obesity, excess salt intake, stress and other reasons. Most often, essential hypertension is recognized in adolescents.

Secondary hypertension in children includes the causes of both transient and chronic hypertension. Most importantly, the cause of hypertension varies with age. The major causes of hypertension in children are of renal origin. The term white coat hypertension denotes the high BP that is detected in clinic/hospital settings but not in ambulatory settings. Though it may well be benign in many,

Table 27.14: Causes of transient hypertension in children

Common causes	Others
<ul style="list-style-type: none"> • Acute post-streptococcal glomerulonephritis • Hemolytic uremic syndrome • Anaphylactoid purpura • Post renal transplant/urological surgery • Hypervolemia • Renal trauma 	<ul style="list-style-type: none"> • Increased intracranial pressure • Guillain–Barré syndrome • Poliomyelitis • Hypernatremia • Corticosteroids/contraceptive administration • Familial dysautonomia • Post coarctation repair

Table 27.15: Causes of chronic hypertension in children**Renal**

- Chronic glomerulonephritis
- Chronic pyelonephritis
- Hydronephrosis
- Vesicoureteral reflux nephropathy
- Malformations of kidney (dysplastic, polycystic, segmental hypoplasia, multicystic kidney)
- Renal tumors

Vascular/renovascular

- Coarctation of aorta
- Umbilical artery catheterization
- Renal artery stenosis
- Renal vein thrombosis
- Renal arteritis with or without aortitis

Endocrine disorders

- Congenital adrenal hyperplasia (11-beta-hydroxylase and 17-hydroxylase defect)
- Cushing's syndrome
- Pheochromocytoma
- Neuroblastoma
- Primary aldosteronism

Other causes

- Intracranial mass
- Hemorrhage
- Essential hypertension.

the observation that exaggerated BP response and increased left ventricular mass in large proportion of the WCH children suggests that it is not an entirely benign condition. Tables 27.14 and 27.15 list the causes of hypertension in children.

Clinical Features

- Clinical features of hypertension depend upon the underlying cause and severity of hypertension.
- Most of the patients with mild hypertension and borderline hypertension and adolescents with essential hypertension may remain asymptomatic and hypertension is recognized during routine medical examinations. Especially in essential hypertension, the blood pressure is only slightly elevated with diastolic pressure at or slightly above the 95th percentile for the age.
- Symptoms attributed to hypertension are headache, nausea, vomiting, dizziness and irritability.
- With severe hypertension, patient may develop hypertension crisis and hypertensive encephalopathy.

Patients may have convulsions, altered sensorium, visual disturbances, persistent vomiting, cranial nerve palsies and other neurological deficits. CCF, though uncommon in children, can develop.

- More than the symptoms of hypertension, the clinical features of secondary causes of hypertension are common in children and they help in proper diagnosis.
 - Renal disorders obviously present with renal symptoms, like polyuria, edema, decreased urine output, etc.
 - Patients with pheochromocytoma present with episodes of palpitation, sweating and flushing.
 - Obesity, buffalo hump, hirsutism and abdominal striae are features of Cushing's syndrome.
 - Hypertensive retinopathy shows specific changes.

Clinically, it is useful to separate mild (grades 1 and 2) from severe retinopathy (grades 3 and 4) as well as prognosis are different for these categories. The presence of exudates and hemorrhages significantly influence the improvement.

- **Grade 1:** Copper-wire appearance of arterioles which assume shape of broad yellow lines.
- **Grade 2:** Thickened arterioles without visible blood column nip the veins.
- **Grade 3:** Hemorrhages and exudates, considerable narrowed arterioles, with a diameter, which is only one-fourth of that of veins, appear as broad white silver lines. Blood column is not visible. Dilatation of vein distal to the artery is apparent.
- **Grade 4:** Papilledema on top of changes seen in grade 3 retinopathy.

Diagnosis

The first and foremost thing in the diagnosis of hypertension is proper recording of the blood pressure. Several recordings are important before labeling a child as suffering from hypertension. Appropriate sized cuffs, appropriate method of recording, and comfortness of the child during blood pressure recording are important.

Mild blood pressure and borderline elevation require close follow-up and repeated measurements. Other associated features help in finding the etiology. Only after confirming hypertension, investigations should be planned. No need to do battery of investigations in all children. Start with investigation for common cause(s) and consider advanced investigations later to confirm the diagnosis. The investigations for hypertension include hemogram, urine analysis, urinary electrolytes, blood urea, nitrogen, serum creatinine, chest X-ray echocardiography, electrocardiography, renal imaging studies, urinary catecholamines, angiography, renal biopsy, plasma renin activity, renal scintiscan, etc.

- **Urine analysis:** One of the most important screening tests and should be done in all cases. Proteinuria, hyaline and granular casts characterize chronic glomerulonephritis. Leucocytes and granular casts indicate pyelonephritis. Hematuria, besides glomerulonephritis, is indicative of many other renal disorders. A 24-hour urinary protein analysis may be required.

- **Urine culture:** As urinary tract infection, either isolated or in association with reflux or obstructive nephropathy is the important cause of hypertension, urine culture should be considered in all cases.
- **Hemogram:** Required as a supportive investigation for the diagnosis of pyelonephritis, hemolytic uremic syndrome, etc.
- **Renal function tests:** Raised blood urea and creatinine are observed in renal disorders. Decreased creatinine clearance suggests diminished glomerular filtration.
- **Serum electrolytes:** Abnormalities in electrolytes are observed in disorders like renal and endocrine causes.
- **Urinary electrolyte:** Helps in diagnosing renal disease including renal tubular disorders.
- **Plasma renin activity:** Increased plasma renin suggests renal or renovascular disorder.
- **Urinary catecholamines:** They are elevated in pheochromocytoma.
- **Chest X-ray:** Useful in the diagnosis of cardiovascular causes like coarctation of aorta. Similarly, electrocardiography and echocardiography help in identifying coarctation of aorta and are helpful in assessing cardiac response to the elevated blood pressure.
- **Renal ultrasonography:** It is a useful noninvasive tool. It helps in evaluating renal parenchyma, diagnosis of hydronephrosis, renal and suprarenal masses.
- **Renal radionuclide scan:** It helps in distinguishing variations in renal perfusion.
- **Renogram:** Rate of uptake and disappearance of I-132-labeled hippuran helps in identification of renovascular disorders.
- **Renal angiography:** It demonstrates lesions in the main arteries or the segmental branches. Doppler ultrasonography may demonstrate arterial and venous blood flow.

Management

Every effort should be made to make a proper diagnosis to optimize the therapy. The treatment of hypertension includes both nonpharmacological and pharmacological treatments. Nonpharmacological treatment includes salt restriction, diet modification, exercise, avoidance of smoking (in adolescents) and control of stress and anxiety. Salt restriction is not practical in younger children. Adolescents with essential hypertension should be counseled about smoking, besides other measures. Dietary modifications and exercise are important in obese children and adolescents, in whose case it is the primary or essential hypertension that is most common.

Pharmacological Therapy

Persistent Hypertension

Patients with persistent hypertension require drugs to control hypertension. Selection of proper drug and appropriate combinations are important for better results. An understanding of the pathology is useful in selecting the drug. Drugs acting at different levels with different mechanisms of actions have to be combined for better

results, especially when long-term drug therapy is required. Various drugs used in the treatment of hypertension include diuretics, vasodilators, angiotensin-converting enzyme inhibitors, centrally acting sympatholytic agents, calcium channel blockers and adrenergic drugs. The dosage schedule is summarized in Table 27.16.

Table 27.16: Antihypertensive drugs: Recommended pediatric dosage

Diuretics

- **Furosemide:** 0.5–2 (maximum 6) mg/kg/day, BID (PO/IV)
- **Spironolactone:** 1–3 mg/kg/day, OD or BD
- **Hydrochlorothiazide:** 1 mg/kg/dose/day, OD or BID
- **Amiloride:** 0.4–0.6 mg/kg/day, OD
- **Metolazone:** 0.2–0.4 mg/kg/day, OD

ACE inhibitors

- **Captopril:** 0.1–0.3 mg/kg/dose (maximum 2 mg/kg/dose), PO, 8 hourly
- **Enalapril:** 0.01 mg/kg/dose PO, BID

Vasodilators

- **Hydralazine:** 0.4–0.8 mg/kg/dose (IV) 2–4 hourly 0.5–2.0 mg/kg (maximum 200 mg/day) PO 6–8 hourly
- **Diazoxide:** 2.5 mg/kg/dose (maximum 100 mg), IV 6–24 hourly
- **Sodium nitroprusside:** 0.5–8.0 mg/kg/min IV infusion. Titrate as required
- **Minoxidil:** 0.2–1.0 mg/kg/day (maximum 50 mg/day), PO OD or BID

Adrenergic blockade agents

- **Propranolol:** 0.25–1.0 mg/kg/dose, PO, 6–8 hourly
- **Labetalol:** 5–10 mg/day, BD 0.2 mg/kg/hr infusion for hypertensive crisis

Sympatholytic drugs

- **L-methyldopa:** 10–40 mg/kg/day BID
- **Clonidine:** 3.5 mg/kg/dose, TID

Calcium channel blockers

- **Nifedipine:** 0.2–0.5 mg/kg/dose (maximum 10–20 mg), PO 300–500 mg/kg/dose, sublingually
- **Verapamil:** 0.15 mg/kg bolus dose followed by 5 mg/kg/min infusion.

- **Diuretics:** Diuretics are an important group of drugs in the management of hypertension, especially in cases of hypertension due to renal disorders. Thiazide diuretics (hydrochlorothiazide, chlorothiazide) are commonly used. They cause hypokalemia, sometimes hyperuricemia and require potassium supplementation. Furosemide is less effective than thiazides and causes profound hypokalemia. Spironolactone is useful in hypertension secondary to adrenal adenoma.
- **Vasodilators and angiotensin-converting enzyme inhibitors (ACE inhibitors):** Vasodilators help in reducing hypertension by reducing afterload. ACE inhibitors are very useful in conditions with excess renin activity. Angiotensin-converting enzyme inhibitors can cause cough, rash, neutropenia, proteinuria and hypotension. Captopril is the most commonly used drug. However, enalapril is more potent and has less adverse effects. ACE inhibitors are more effective when used in combination with diuretics. Hydralazine can cause tachycardia, drug-induced lupus erythematosus. Minoxidil is associated with hirsutism and fluid retention.
- **Calcium channel blockers:** Calcium channel blockers cause vasodilatation and increase the excretion of sodium. They can cause facial flushing, tachycardia, and hypotension.
- **Sympatholytic agents:** Alpha methyldopa and clonidine are centrally acting antihypertensive agents. They can cause sedation (methyldopa), lupus-like syndrome, hepatitis and postural hypotension. They are a useful group of drugs in the management of hypertension.

Acute Severe Hypertension

Acute severe hypertension (hypertensive crisis) may be in the form of hypertensive urgency (without target organ damage) or emergency (with target organ damage). Both need aggressive, well-monitored intravenous antihypertensive medication (Table 27.17). The aim is to reduce the BP by upto

Table 27.17: Antihypertensive drugs for severe hypertension

Drug	Dosage	Special comments
Sodium nitroprusside	0.5–10 µg/kg/min in 5% dextrose	Since it may cause cyanide toxicity, cyanide levels should be monitored when used for >72 hourly and in renal failure. Else coadminister with sodium thiosulfate
Labetalol	IV bolus: 0.20–1.0 mg/dose q5–10 min (maximum 40 mg) IV infusion: 0.25–3.0 mg/kg/hourly	ADRs include pallor, abdominal discomfort, diarrhea, bradycardia. Hypotension (orthostatic). Avoid in overt heart failure and bronchial asthma
Nicardipine	IV bolus: 30 µg/kg (maximum 2) mg/dose q 15 min IV infusion: 0.5–4.0 mg/µg/kg/min (maximum 5 mg/hr)	ADRs include reflex tachycardia, flushing, nausea, headache, raised ICP, phlebitis
Clonidine	15–25 mcg/kg/day q 6–8 hourly orally.	ADRs include dryness of mouth and drowsiness (somnolence)
Minoxidil	0.1–0.2 mg/kg/dose	Very powerful, long-acting oral direct vasodilator
Nitroglycerine	1–3 µg/kg/min	ADRs include headache, tachycardia, methemoglobinemia
Phentolamine	0.1–0.2 mg/kg; may be repeated q2–4 hourly	Abdominal discomfort, reflex tachycardia
Hydralazine	0.2–0.6 mg/kg/dose IV, IM	If given as IV bolus, it should be every 4 hourly
Esmolol	IV infusion (preferably constant) 100–500 µg/kg/min	ADRs include profound bradycardia
Nifedipine	0.2–0.5 mg/kg/dose 4–6 hourly with a maximum dose of 10 mg	ADRs include sudden fall in BP (excessive), peripheral edema

Abbreviations: IV, intravenous; PO, per os (by mouth or orally); ADR, adverse drug reaction; ICP, intracranial pressure; IM, intramuscular; BP, blood pressure.

502 25% in the first 8 hours; out of this, 10% reduction should be in the first hour. The remaining 75% reduction needs to be achieved gradually in the next 36–48 hours. Cerebral ischemia may occur in case of too rapid reduction in BP.

Admit the patient in pediatric intensive care unit. Stabilize airway, breathing and circulation, if required. Select appropriate anticonvulsants. The drugs of choice are intravenous labetalol, sodium nitroprusside or, when neither is available, sublingual/oral nifedipine.

Start with intravenous labetalol or sodium nitroprusside infusion and titrate the rate of infusion depending upon the response. While patient is on high-dose infusion, sudden profound hypotension can develop and, hence, very close monitoring and titration of the drug is required. In the event of hypotension, stop the infusion and then decide depending upon the blood pressure levels whether to continue or not and also consider using alternative drugs. Sublingual nifedipine has very short duration of action and is not an ideal drug in hypertensive crisis. However, while arranging for labetalol or sodium nitroprusside or other drugs and when other drugs are not available, nifedipine can be tried with caution, ensuring that blood pressure does not fall abruptly.

Alternatively, intravenous hydralazine or diazoxide may be used. Once the blood pressure levels are reduced and remain stable for some time, start on oral antihypertensive drugs and withdraw parenteral drugs. Hypertensive crisis due to pheochromocytoma requires use of alpha adrenergic blocking agents like phentolamine (1–2 mg IV and effect starts in about a minute). Propranolol should be added only after starting alpha adrenergic blockers. Otherwise it causes rebound hypertension.

In case of secondary hypertension, over and above antihypertensive drug(s), underlying disease (say, chronic renal disease, pheochromocytoma, coarctation of aorta, hyperthyroidism, etc.) should also be treated. Figure 27.31 provides an algorithmic stepped care approach to antihypertensive treatment.

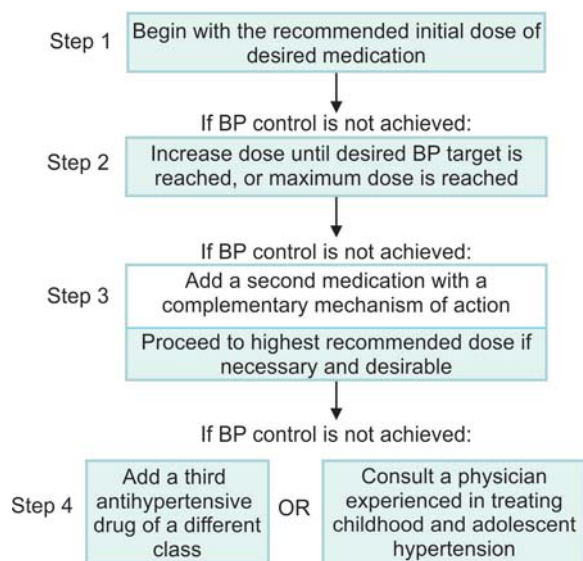


Fig. 27.31: Algorithmic stepped care approach to antihypertensive treatment.

Course and Prognosis

Poorly controlled hypertension predisposes to many hypertension-related problems including stroke, and ischemic heart disease.

Adolescents detected to have essential hypertension are likely to continue to have hypertension as adults. In cases of secondary hypertension, the prognosis is dependent on the underlying disease and its natural course. The prognosis of surgically corrected coarctation is variable. The prognosis in cases of chronic renal disease depends upon the response to dialysis and transplant. Neonates who develop hypertension due to umbilical artery catheterization have favorable outcome with most of them improving.

Prevention

Hypertension can be prevented with changes in the life-style (including food modifications, exercise, and restricting high salt intake aimed at safeguarding from obesity), and avoidance of smoking and alcohol in adolescents. The prevention of secondary hypertension requires primary prevention mainly and appropriate secondary preventive measures.

INTERVENTIONAL CARDIAC PROCEDURES

Interventional cardiology is defined as a nonsurgical treatment of certain cardiac defects that until recently needed open heart surgery. Valvular pulmonary stenosis, aortic stenosis, PDA, secundum ASDs, etc. fall in this category.

As a result of availability of interventional cardiac procedures, such as balloon valvuloplasty (Fig. 27.32) and radio-frequency ablation technique, outlook for several CHDs has improved considerably. The indications for various interventional procedures are summarized in Table 27.18. An intervention cardiac procedure has to be performed in consultation with a cardiac surgeon.

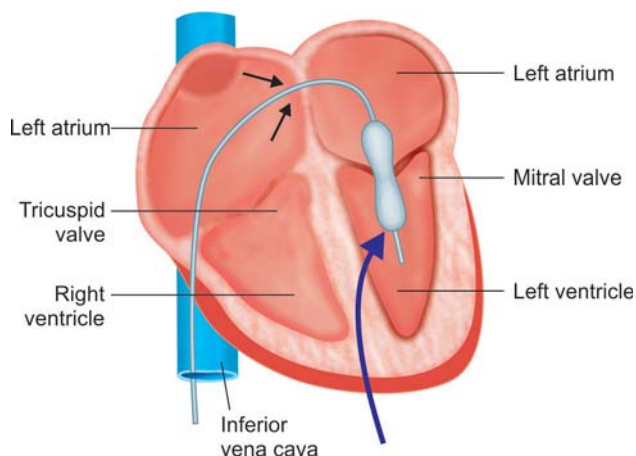


Fig. 27.32: Balloon valvuloplasty. A thin catheter with a small, deflated balloon at its tip (balloon-tipped catheter) is inserted through the skin in the groin area into a blood vessel. It is further threaded up to the opening of the narrowed heart valve. Then the balloon is inflated to stretch the valve open and relieve the valve obstruction.

Table 27.18: Indications of various interventional cardiac procedures

Procedure	Indications
Balloon valvuloplasty	<ul style="list-style-type: none"> • Stenotic valves: Aortic stenosis, mitral stenosis • Narrow arteries: Coarctation of aorta, obstructive aortoarteritis • Venous obstruction: Superior/inferior vena cava obstruction
Closing of abnormal openings	VSD, ASD
Closing of arterial channels	PDA, aortopulmonary collaterals in TOF, surgically created shunts in Fallot's physiology, coronary arteriovenous fistula, systemic arteriovenous fistula, pulmonary arteriovenous fistula
Radiofrequency ablation techniques	Arrhythmia management

Abbreviations: VSD, ventricular septal defect; ASD, atrial septal defect; PDA, patent ductus arteriosus; TOF, tetralogy of fallot.

Multiple Choice Questions

- Characteristics of an innocent murmur include all of the following, except:
 - Occurs during ejection
 - Musical and brief
 - Tendency to be better heard as the child grows
 - Attenuated in the sitting position
 - Intensified by pyrexia, excitement and exercise
- Spot the wrong observation:
 - Cardiothoracic ratio is more dependable in later childhood rather than in infancy
 - Overloading of circulation, as in overhydration, or severe chest infection, may cause heart failure at any age
 - Digoxin is now believed to have only subservient role in management of heart failure
 - Rheumatic heart disease has virtually been eliminated from Indian subcontinent
 - Chromosomal defects, say Down syndrome, trisomy 13, trisomy 18, Turner syndrome, etc., are usually accompanied by congenital heart disease
- All of the following regarding spontaneous closure/correction of congenital septal defects, are true, except:
 - Small ASD and VSD usually close by 3 years of age
 - PDA, if it have a spontaneous closure, will do so in the first 2-4 weeks only
 - Muscular VSD has greater chances of closure than membranous VSD
 - ASD involving fossa secundum (not fossa ovalis) may close spontaneously
- Which of the following heart disease is known for causing brain abscess as its complication?
 - Transposition of great arteries
 - Ventricular septal defect
 - Tetralogy of Fallot
 - Aortic stenosis
 - Rheumatic heart disease
- Spot the wrong matching

A. Egg-on-side appearance	Transposition of great arteries
B. Figure of "8" or snowman appearance	Total anomalous venous return
C. Boot-shaped heart	Tetralogy of Fallot
D. Water-bottle appearance	Pericardial effusion
E. Dinner-fork sign	Ventricular septal defect
- Wide pulse pressure is a feature of each of the following, except:
 - Patent ductus arteriosus
 - Arteriovenous fistula
 - Hypothyroidism
 - Pulmonary stenosis
 - Ventricular septal defect with aortic regurgitation
- Causes of transient hypertension include each of the following, except:
 - Pheochromocytoma
 - Acute glomerulonephritis
 - Henoch-Schönlein purpura
 - Hypernatremia
 - Renal vein thrombosis

contd...

8. Features of cardiac tamponade include each of the following, except:
 - A. Pulsus paradoxus
 - B. Bradycardia
 - C. Raised JVP
 - D. Narrow pulse pressure
 - E. Paradoxical inspiratory filling of neck veins
9. Which one is an unlikely cause of secondary cardiomyopathy?
 - A. Beriberi
 - B. Mucopolysaccharidosis
 - C. Nutritional marasmus
 - D. Cystic fibrosis
 - E. Sickle cell disease
10. "E" sign in imaging is a feature of:
 - A. Aortic stenosis
 - B. Mitral stenosis
 - C. Aortic regurgitation
 - D. Coarctation of aorta
 - E. Tricuspid atresia

Answers

- | | | | | | |
|------|------|------|-------|------|------|
| 1. C | 2. D | 3. D | 4. C | 5. E | 6. D |
| 7. A | 8. B | 9. C | 10. D | | |

Clinical Problem-solving**Review 1**

A 14-year-old girl, who had been treated for acute rheumatic carditis with heart failure with medications, including steroids and aspirin, some 6 months back and has been on irregular benzathine penicillin presents with prolonged fever of 15 days' duration with splenomegaly and splinter hemorrhages below nail beds and petechiae over skin and buccal mucosa. Hb 8.2 g/dL. CRP positive. Urine: microscopic hematuria.

1. What in your opinion, is the most logical diagnosis?
2. How to confirm the clinical diagnosis?
3. Any alternative means of confirming the diagnosis?
4. What are the predisposing risk factors?

Review 2

A 2-year-old child presents with persistent heart failure (refractory to standard medication) with a history of right-sided hemiplegia a year back. A pansystolic murmur is best heard at the apex with radiation to the back, Chest X-ray and echocardiography shows cardiomegaly without any structural abnormality.

1. What is your diagnosis?
2. Any findings expected in ECG?
3. Since the patient's heart failure is refractory to standard medication, any special investigation needed?
4. Is hemiplegia an odd feature in such a patient?

Review 3

A 7-year-old child being investigated for recurrent chest infection is found to have a parasternal impulse, a systolic thrill over second left interspace, second sound widely split with ejection systolic murmur in second and third left interspace. CXR shows slight cardiomegaly.

1. What is the most probable diagnosis?
2. What is the EEG manifestation of ostium primum defect?
3. Can this patient develop pulmonary arterial hypertension as a complication?
4. When should such a patient have surgical correction?

contd...

Answers**Review 1**

1. The clinical profile eminently fits into the diagnosis of infective endocarditis.
2. The gold-standard for establishing diagnosis of infective endocarditis is blood culture. Ideally, 3–5 blood samples collected separately from different aseptically prepared sites are needed.
3. Echocardiography showing vegetations (>2 mm) is important complementary as well as when cultures turn out to be negative.
4. Predisposing risk factors for endocarditis include underlying congenital or acquired heart disease (as in the case in review), recent cardiac surgery, prosthetic heart valve, cardiac catheterization, dental procedures, sepsis, etc.

Review 2

1. Dilated (congestive) cardiomyopathy is the most probable diagnosis.
2. ECG is likely to show nonspecific changes in ST and T, often with left ventricular hypertrophy. Arrhythmias may be present.
3. Myocardial biopsy.
4. No. Thromboembolic complications are well-known in dilated cardiomyopathy.

Review 2

1. The clinical profile of this 7-year-old child is in keeping with the diagnosis of atrial septal defect .
2. ECG shows RVH and right axis deviation.
3. Yes, pulmonary arterial hypertension is a well known complication of ASD.
4. Surgical correction in ASD is best done in childhood, preferably before school entry.

FURTHER READING

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INTRODUCTION

Neurological disorders show a wider and more diverse spectrum in infancy and childhood than in adulthood. In addition, congenital neurological disorders, residual birth injuries, birth asphyxia, seizure disorders and central nervous system (CNS) infections have special significance in pediatric practice.

DEVELOPMENTAL ASPECTS

At the very outset, it is important to briefly recall that development of the CNS occurs in three stages.

1. In the first stage, the so-called **cytogenesis**, the genetic and chromosomal disorders, malformations and inborn errors of metabolism express themselves
2. In the second stage, the so-called **histogenesis**, the disorders like agenesis of corpus callosum, tuberous sclerosis, etc. express themselves
3. In the third stage, the so-called **organogenesis**, is determined by the eventual shape of the CNS.

Fault in blending of the neural and extraneural tissues results in arteriovenous malformations. When neural tissue develops a faulty blending with the ectodermal tissue, hamartoma, craniopharyngioma, etc. may occur. Porencephaly or hydranencephaly may follow destructive or inflammatory lesions of the brain.

NEUROLOGICAL EVALUATION

Clinical Work-up

Evaluation of CNS must begin with an accurate history followed by examination conducted with patience, tact and observations. Special attention must be paid to examination of head, cranial nerves, motor system, sensory system, gait, etc. Fundoscopy should be considered an essential component of neurological examination, especially before doing lumbar puncture (LP). Also, See Chapter 2 (Pediatric History-taking and Physical {Clinical} Examination).

Soft Neurological Signs

The so-called **soft neurological signs** (SNS) deserve a special emphasis. These are defined as particular forms of deviant performance on a motor or sensory test in the neurological examination, which is abnormal for a particular age. Box

Box 28.1 Soft neurological signs

- Mirror movements
- Head bobbing/foot tapping
- Dysdiadochokinesia
- Finger agnosia
- Stimulus extinction
- Choreiform movements
- Lateral dominance
- Verbal dyspraxia
- Strabismus.

28.1 provides the list of soft neurological signs. One must exercise significant caution in testing the presence of these signs. It may mean observation of a series of timed motor tasks as also comparison of the patient's movements with those of normal children of similar age and sex.

The interpretation of a soft neurological sign is also problematic. It may well be present in an intellectually normal child. Yet, presence of two or more such signs in a child points to a neurological dysfunction in the form of behavior, coordination and learning difficulties.

According to one school of thought, SNS represent a developmental lag rather than a fixed neurological abnormality (the earlier view). Such a dysfunction could well be cerebral palsy (CP) or simply an attention deficit or learning disorder. Therefore, rather than jumping at giving the child a label of a development disability, the child should be monitored closely. The cornerstone of a neurological examination is localization of the lesion. Unfortunately, SNS fail to help us here. On the other hand, hard signs (tendon reflexes, Macewen sign*) decidedly do so!

Investigative Work-up

Cerebrospinal Fluid

- **Lumbar puncture and cerebrospinal fluid** (CSF) examination are mandatory for confirming the diagnosis of meningitis, encephalitis and subarachnoid hemorrhage. These also assist in the evaluation of the demyelinating, degenerative and collagen vascular disorders and the presence of tumor cells
- **Subdural tap** is indicated for confirming the diagnosis of subdural effusion or hematoma.
- **Ventricular tap** is indicated for removal of CSF in life-threatening raised intracranial pressure (ICP) provided that the conservative measures to reduce it have failed.

* After Sir William Macewen (1848–1924), a surgeon and professor of the University of Glasgow, Scotland. "Macewen" should be pronounced as ma-k-en.

Neuroimaging

- **Skull X-ray** is a useful procedure for demonstrating skull fracture, intracranial calcification, craniosynostosis, bony defects, congenital anomalies or RIP.
- **Cranial ultrasound** is of value in the infants with a patent anterior fontanel in delineating hemorrhage, hydrocephalus, and tumor. In older children, it may be employed for placement of a shunt, location of a small tumor and for direction of needle biopsy.
- **Computed tomography (CT)** scanning, a noninvasive procedure that makes use of conventional X-ray techniques, has revolutionized the neurologic evaluation. It is of special value in demonstrating congenital anomalies (porencephalic cysts, hydrocephalus), subdural collection, calcification, hematoma, tumor, and areas of cerebral edema, infarction and demyelination. CT scanning is not quite useful in delineating lesion of posterior fossa and spinal cord.
- **Magnetic resonance imaging (MRI)**, another noninvasive procedure that does not utilize ionizing radiation (hence totally free of biological risk), is of special value in delineating neoplasm, cerebral edema, degenerative diseases and congenital anomalies. Unlike CT scanning, it is capable of delineating lesions of posterior fossa and spinal cord. It cannot detect intracerebral calcification.
- **Functional scans**, say positron emission tomography (PET) and single photon emission computed tomography (SPECT) are important presurgical investigations in intractable epilepsy, cerebral tumors and head injury.
- **Cerebral angiography**, using digital subtraction technique, is especially of value in delineating arteriovenous malformations, aneurysms, arterial occlusions and venous thrombosis
- **Pneumoencephalography** is of value in delineating prepontine and chiasmatic cisterns.
- **Myelography** is useful in demonstrating spinal cord compression, e.g. congenital anomalies, tumors, vascular malformations, etc. The procedure requires injection of a contrast material into the subarachnoid space, resulting in arachnoiditis at times. Currently, MRI is believed to be superior to contrast myelography in a majority of the situations.
- **Digital subtraction cerebral angiography** contributes to evaluation of cerebrovascular disorders.
- **Carotid Doppler studies** are useful in evaluating the flow patterns.

Electroencephalography

Electroencephalography (EEG) is of value in evaluation of paroxysmal neurologic disorders, say epilepsy. EEG waves may be graded as delta (1–3 per sec), theta (4–7 per sec), alpha (8–12 per sec), and beta (13–20 per sec). Many factors like age, state of alertness/wakefulness, eye closure, medication and disease tend to cause alteration in these waves.

- Spikes and slow waves are usually indicative of epilepsy
 - Focal spikes may be manifestation of irritative lesions, say cysts, slow-growing tumors and glial scar tissue
 - Slow focal waves may point to existence of a circumscribed lesion, say a hematoma, tumor, infarction or localized infectious process
 - Generalized slow waves point to a metabolic, inflammatory or more widespread process.
- Limitations of EEG include:
- Normal records in interictal periods
 - Abnormal record even in some normal individuals
 - Failure to assist in decision-making about discontinuing/stopping anticonvulsant therapy.
- EEG or polygraphic video monitoring is of great help in:
- Precise delineation of types of seizures and thus exact medical or surgical management
 - Differentiating epilepsy from epilepsy-like states
 - Study of efficacy of various therapeutic measures
 - Characterization of seizures in neonates.

Evoked Potential Response

Evoked potential, an electrical response that follows stimulation of CNS by specific stimulus of the visual, auditory or sensory system, is beginning to find increasing application.

Visual evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs), and somatosensory evoked potentials (SSEPs) can detect visual, auditory and spinal cord functions in neonates, in comatose individuals and during operative procedures.

Biopsy

Biopsy of neurogenic tissues such as nerve, ganglion cells of rectum, or brain may be useful in metabolic and degenerative disorders.

Psychometric Tests

Psychometric tests are useful for evaluating the cognitive ability and intelligence of a suspected case of mental retardation.

Electroretinography

Electroretinography is useful in evaluation of degenerative disorders of retina.

Electromyography

Electromyography is useful in evaluation of neuromuscular disorders. It is of particular help in characterization of muscle disorders. In a floppy infant, it clarifies whether the cause is neurogenic or myogenic.

Nerve Conduction Studies

These are useful in evaluation of peripheral neuropathies (poliomyelitis versus Guillain-Barré syndrome {GBS} and degenerative disorders involving peripheral nervous system metachromatic leukodystrophy).

NEURAL TUBE DEFECTS

(Myelodysplasia, Dysraphism)

Neural tube defects (NTDs) are responsible for an overwhelming number of developmental anomalies of the

Box 28.2 Maternal risk factors for neural tube defects

- Radiation
- Drugs and chemicals—alcohol, sodium valproate, carbamazepine
- Diabetes mellitus (insulin-dependent)
- Malnutrition—zinc and folic acid deficiency
- Genetic determinates, alone or in one or the other combination—Trisomy 13 and 15.

Box 28.3 Risk of neural tube defects in subsequent pregnancies

- First subsequent pregnancy—3.5%
- Second subsequent pregnancy—10%
- Third subsequent pregnancy—25%

CNS. Risk of such defects is 1.5 in 1,000 live births. Risk in subsequent pregnancy is as high as 50 in 1,000 live births.

Etiopathogenesis

They result from a failure of the neural tube (plus its covering mesoderm and ectoderm) to close in utero between third and fourth week of gestation.

Folic acid deficiency in the mother has emerged as the most important factor in causation of NTDs. Maternal factors that adversely affect the normal development of the neural tube, thereby causing the NTDs are listed in Box 28.2. Magnitude of risk of NTDs in subsequent pregnancies is shown in Box 28.3.

Types

- **Spina bifida occulta** is the most frequent and the most benign NTD. A dimple, tuft of hair, dark spot or swelling over the site of gap in the spine (Fig. 28.1), points to its presence. Often, it is detected on an X-ray of the spine that reveals a defective closure of the posterior arch and laminae of the vertebrae, usually L5 and S1.

Most of the cases are asymptomatic. In an occasional case, loss of bladder and bowel control and cavus



Fig. 28.1: Spina bifida occulta. Note a tuft of hair on the lower back. This is one of the typical signs of spina bifida occulta.



Fig. 28.2: Meningocele. The midline sac transilluminates easily. Usually, it is asymptomatic and well covered with skin.

deformities of feet develop as the child grows. More significant anomalies of the spinal cord (say diastematomyelia, tethered cord, syringomyelia, etc.) may coexist with spina bifida occulta in a small proportion of the cases. Progressive neurologic abnormality is an indication for a surgical correction

- **Meningocele** is a fluctuant midline sac of meninges that herniates through a defect in the posterior vertebral arch, generally in the low back (Fig. 28.2). It transilluminates easily. Usually, it is asymptomatic and well covered with skin.

Associated anomalies include hydrocephalus, diastematomyelia, tethered cord and lipoma.

Surgery may be delayed unless there are neurological symptoms, skin covering is thin, or CSF leak is present

- **Meningomyelocele** (myelomeningocele) is a midline cystic sac of meninges and spinal tissue that herniates through a defect in the posterior vertebral arch, usually in the lumbosacral region though it may be located anywhere along the neuroaxis (Fig. 28.3).

It transilluminates less easily, is covered with only a thin skin, and is usually accompanied by a neurological deficit (say flaccid paralysis, absent drop reflexes and absent sensations) and such postural abnormalities as club foot and subluxation of the hips. In case of meningomyelocele of the thoracic or cervical region, neurologic signs are in the form of spasticity and very brisk reflexes. Hydrocephalus is a common association. Risk of rupture of the sac with superadded infection and meningitis is high.

It is a sound principle to aggressively repair the meningomyelocele followed by a shunting procedure if hydrocephalus coexists with it

- **Encephalocele** (Fig. 28.4) is a meningeal sac together with cerebral cortex, cerebellum, or portions of the brainstem herniating through a bony defect in the skull



Fig. 28.3: Meningocele. It transilluminates poorly because of a solid neurogenic tissue within it, is covered with only a thin skin, and is usually accompanied by a neurological deficit.



Fig. 28.4: Encephalocele. The meningeal sac, usually in the occipital region, contains brain tissue which herniated through a defect in the skull.

(cranium bifidum), usually in the occipital region. The size may vary from small to as big as exceeds the cranium.

There is high risk of developing hydrocephalus due to aqueduct stenosis or a Chiari malformation and Dandy-Walker syndrome. Association of occipital encephalocele with cleft lip or palate, microcephaly, abnormal genitalia, congenital nephrosis and polydactyly is termed **Meckel-Gruber syndrome**.

Prognosis is poor. Most of the patients develop visual problems, seizures, mental retardation and microcephaly. Prenatal diagnosis is possible by estimation of alpha-fetoprotein level and biparietal diameter on ultrasonography.

- **Anencephaly** is a rudimentary brain with a large defect of the calvarium, meninges and scalp. Folding of the ears, cleft palate and congenital heart disease coexist in some 15% of the cases.

In half of the anencephalic pregnancies, there is history of polyhydramnios. Death usually occurs within a week or two of birth.

- **Diastematomyelia** is a projection of bony or fibrocartilaginous septum from the posterior vertebral body that divides the spinal cord into two halves. The most common site is L1, L2 and L3. It is usually accompanied by such abnormalities of the vertebral bodies as fusion defects, hemivertebrae, hypoplasia, kyphoscoliosis, and spina bifida (including meningocele).

The presence of a localized midline tuft of hair, dermal sinus, hemangioma, etc. should arouse suspicion of existence of this anomaly.

In symptomatic cases, there is weakness and muscle atrophy in lower limbs and urinary incontinence. Excision of the bony spur and lysis of surrounding adhesions are indicated in symptomatic cases.

- **Tethered spinal cord** is the persistence of conus modularis as a thickened rope-like filum terminated at or beyond the L2 level (normally it ends at L1), producing neurological signs sooner or later. A midline skin lesion like lipoma, tuft of hair, dermal pit, hemangioma or a hyperpigmentation patch may provide a clue to the presence of this anomaly. Association with diastematomyelia is well known. Frequently, talipes equinovarus (clubfoot) accompanies it. Surgical excision of the terminate is warranted to halt the progression of the neurologic signs.

- **Syringomyelia** is a cystic cavity within the spinal cord. It may communicate with the CSF pathway (syringobulbia). Communicating syringomyelia is usually complicated by Chiari type 1 malformation. In it, CSF passes caudally on sneezing or coughing, producing dilatation of the central canal.

Noncommunicating syringomyelia is complicated by cord tumors, trauma, vascular accidents and arachnoiditis. Syringomyelia progresses slowly, producing symptoms in later childhood or adulthood.

Manifestations include a progressive scoliosis, dissociation of sensations (loss of pain and temperature, preservation of light touch), trophic ulcers, muscle wasting, absent deep reflexes in upper limbs and upper motor neuron signs in lower limbs.

Treatment includes decompression, plugging the open end of the central canal, percutaneous aspiration and draining the cystic cavity into subarachnoid space.

- **Lissencephaly** (agyria) manifests with failure to thrive, microcephaly, gross developmental delay and seizures, often in association with ocular anomalies, distinctive facies with prominent occiput, broad forehead and anteverted nostrils.

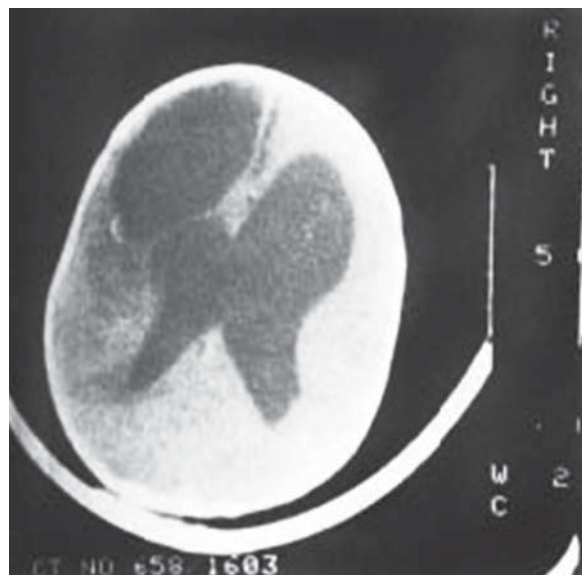


Fig. 28.5: Computed tomography scan demonstrating porencephalic cysts in left frontal region.

Remarkable absence of sulci and smooth brain are the noteworthy CT scan findings.

- **Schizencephaly** denotes presence of clefts within the cerebral hemisphere which may be fused or unfused and unilateral or bilateral. Manifestations include severe mental retardation, seizures, microcephaly and spastic quadriparesis. CT scan is diagnostic in delineating the size and shape of the cleft.
- **Porencephaly** means presence of cavities or cysts (Fig. 28.5) within the brain in the region of Sylvian fissure. They communicate with subarachnoid space, the ventricular system, or both. Manifestations include microcephaly, mental retardation, seizures, quadriparesis and optic atrophy.
- **Agenesis of cranial nerves** may include II, III, V, VIII, IX, X, XI and XII nerves. In the so-called **Mobius syndrome**, there is facial weakness (bilateral) and feeding difficulty presenting in neonatal period.
- **Agenesis of corpus callosum** may be present as an inherited X-linked trait or as a component of a specific chromosomal disorder like trisomy 8 and trisomy 18.
- **Acardi syndrome**, a rare disease of females, is characterized by a trio of infantile spasms, chorioretinopathy and agenesis of corpus callosum. Additional features include vertebral and costal anomalies (fusion of vertebral bodies, hemivertebrae, scoliosis, spina bifida, fused ribs) and subependymal heterotopies. Motor and mental retardation is apparent at early age. The cause appears to be a newly mutated X-chromosomal dominant gene lethal to males in utero. CT scan detects agenesis of corpus callosum. Prognosis is poor, most patients dying early in life.

Prenatal Diagnosis

Prenatal screening of maternal serum for alpha-fetoprotein is currently the most effective method for identifying at-risk pregnancies in relation to NTD in utero.

Prevention

Periconceptual folic acid is the most important primary prevention. It acts not by just correcting the deficiency but also by overcoming an enzymatic block (deficiency of enzyme 5-methyltetrahydrofolate because of partial block in conversion from 5, 20-methylenetetrahydrofolate) in homocysteine metabolism.

- Periconceptual folic acid, 0.4 mg* OD orally (1 month before and 2 months after conception) to all mothers (primary prevention).
- Periconceptual folic acid, 5 mg OD orally, after the birth of a defective baby (or at least 2 months before next conception) till 3 months after the conception (secondary prevention).

Supplements of zinc, biotin and vitamin A may also be given.

PSEUDOTUMOR CEREBRI

(Benign Intracranial Hypertension, Otitic Hydrocephalus)

Definition

By definition, this condition is a RIP without any biochemical or cellular CSF abnormalities and yet producing manifestations that simulate those of an intracranial space-occupying lesion such as a brain tumor. Generally, it is more or less a benign and self-limiting condition.

Clinical Features

- Manifestations include bulging fontanel, papilledema, changes in sensorium, headache, convulsions, vomiting and other neurological abnormalities like sixth nerve paralysis and ataxia
- There is, as a rule, no evidence of focal neurological deficit
- If the high pressure continues, optic atrophy and blindness may follow.

Etiopathogenesis

Raised ICP results from diffuse cerebral edema. The pathogenesis is not clear. Various explanations include:

- Alterations in CSF absorption and production
- Cerebral edema
- Erroneous vasomotor control
- Erroneous cerebral blood flow
- Venous obstruction.

Various causes of pseudotumor cerebri are given in Box 28.4.

* Though 0.4 mg (400 µg) dose of folic acid is good enough for primary prevention, in practice use of 5 mg is an accepted practice. Folic acid is by and large safe even in high doses.

Box 28.4 Etiology of pseudotumor cerebri

Metabolic: Galactosemia, hypoparathyroidism, pseudohypoparathyroidism, hypophosphatasia, prolonged steroid therapy, sudden withdrawal of steroid therapy, hypervitaminosis A, hypovitaminosis A, Addison disease, obesity, cystic fibrosis growth hormone therapy, menarche, contraceptives, pregnancy

Infections: Chronic otitis media, mastoiditis, roseola infantum, GBS

Hematologic: Iron-deficiency anemia (chlorosis), lead poisoning, hemolytic anemia, polycythemia, Wiskott-Aldrich syndrome

Drugs: Nalidixic acid, tetracyclines, nitrofurantoin, DPT vaccine

Obstructive: Lateral sinus thrombosis, posterior sagittal sinus thrombosis, obstruction of superior vena cava, head injury

Collagenosis: SLE

Nutritional: Overenthusiastic dietetic therapy in malnutrition.

Abbreviations: GBS, Guillain-Barré syndrome; DTP, diphtheria, tetanus, and pertussis; SLE, systemic lupus erythematosus.

Treatment

Pseudotumor cerebri is a self-limiting condition. RIP may persist for several months. If RIP is of high magnitude, there is a risk of chronic compression causing optic nerve damage.

- Attempts to remove the supposedly offending factor and reduce ICP should be made in patients with grossly raised pressure
- Repeated LPs, restriction of fluids, hypertonic solutions and diuretics (acetazolamide, 30–50 mg/kg/day) are justified
- Steroids
- Surgical decompression by removing subtemporal bone flap
- Weight reduction in obese children is mandatory.

ACUTE STROKE SYNDROMES

(Acute Hemiplegia of Childhood, Acute Infantile Hemiplegia, Pediatric Stroke)

Definition

Acute stroke syndrome is defined as an occurrence of hemiplegia following arterial thrombosis/embolism, venous thrombosis, intracranial hemorrhage, etc.

Types

- Occlusive cerebrovascular disease:
 - **Arterial thrombosis and embolism:** It follows involvement of major cerebral arteries (internal carotid, anterior, middle and posterior cerebral) or smaller cerebral arteries. Blunt trauma to posterior pharynx and acute angulation of the artery are important causes of internal carotid artery thrombosis followed by shedding of emboli from the thrombi. Manifestations include a progressive flaccid hemiplegia, aphasia if dominant hemisphere is involved and focal motor seizures.
 - **Venous thrombosis:** It may follow sepsis (meningitis, otitis media, cavernous sinus thrombosis) or

nonseptic conditions (hypercoagulopathy, cyanotic congenital heart disease, iron deficiency anemia, and leukemia) and is characterized by dilated scalp veins, bulging anterior fontanel and manifestations of increased ICP.

- **Intracranial hemorrhage:** The underlying conditions are arteriovenous malformations and rarely cerebral aneurysms.
 - **Subarachnoid hemorrhage** is characterized by severe headache, neck rigidity and progressive deterioration in sensorium.
 - **Intracerebral hemorrhage**, usually seen in pre-term infants, is characterized by focal neurologic signs and seizures.
- **Inflammatory disease:** Granulomatous lesions
- **Porencephaly:** Intracranial space-occupying lesions (ICSOL), brain abscess, meningoencephalitis, meningitis
- **Mitochondrial disease:** MELAS*
- **Idiopathic:** Exact etiology remains elusive despite extensive investigative work-up.

Differential Diagnosis

It is from stroke-like events such as:

- Alternating hemiplegia of childhood
- Todd paralysis
- Metabolic diseases (homocystinuria)
- CNS infections (meningitis, encephalitis, etc.)
- Hematological disorders (coagulopathies, sickle-cell disease, thrombocytopenia)
- Lipid abnormalities
- Vasculitis/connective tissue disorders
- Cerebral tumors.

If, despite good history and physical examination plus CT scan (Fig. 28.6) and/or MRI, cerebral angiogram,

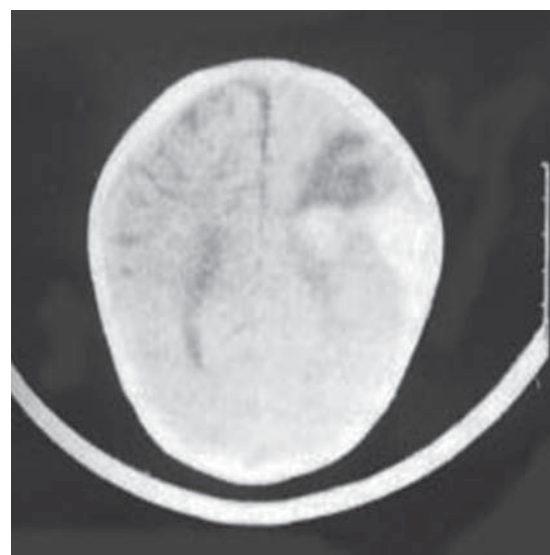


Fig. 28.6: Computed tomography scan showing intracerebral hemorrhage in a child with left-sided hemiplegia.

* MELAS stands for mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes. It is one of the group of mitochondrial cytopathies.

- 512** electrocardiogram (ECG), electroencephalogram (EEG), etiologic diagnosis remains unclear, basic investigation should be carried out to exclude differentials.

Treatment

Supportive measures include attention to airway, breathing and circulation (ABC), fluid management, maintenance of normoglycemia and control of fever and seizures. Role of thrombolytic therapy (aspirin, heparin, T-plasminogen activator) in pediatric stroke remains unclear. Calcium channel blockers, vasodilators, platelet inhibitors, free radical scavengers and coenzyme-Q may be considered.

Prophylaxis

Prophylaxis against recurrence(s) includes:

- Heparin (low molecular weight) for several months
- Aspirin
- Regular blood transfusions in sickle-cell disease
- Immunosuppressant therapy in vasculitis.

Prognosis

It varies with etiological condition. In idiopathic infantile hemiplegia, chances of recurrent episodes of seizures (epilepsy) and mental retardation are high.

BELL PALSY

(Peripheral Facial Palsy)

Definition

This is an isolated acute unilateral seventh cranial nerve palsy of peripheral (lower motor neuron) type in which the etiology is unexplained.

Etiopathogenesis

Viral infections, e.g. Epstein-Barr virus (most common), herpes virus, mumps virus, etc. and Lyme disease may possibly be responsible for the lower motor neuron lesion of the facial nerve.

Clinical Features

Manifestations include:

- Deviation of the upper and lower face to opposite side
- Drooling at the angle of the mouth
- Inability to close the eye, on affected side (Fig. 28.7)
- Loss of taste in anterior two-thirds of the tongue.

Diagnosis

- It is more or less clinical.
- Electrophysiological examination of the facial nerve may help to find out the extent of neuropathy and degeneration.
- In chronic cases (not recovering in few weeks), causes of facial nerve involvement such as leukemia, tumors, brainstem infarct and injury must be ruled out.

Treatment

Treatment in acute cases is more or less supportive. An ocular lubricant, especially at night, is needed for



Fig. 28.7: Bell palsy. Note the inability to close the right eye.

protection of the cornea. A short course of prednisolone (1 mg/kg/day × 1–2 weeks) is justified.

Prognosis and Outcome

Over 85% cases show full recovery spontaneously. In 10% cases, the patient may be left with slight weakness. In the remaining 5% cases, permanent severe facial weakness may persist.

ACUTE FLACCID PARALYSIS

The term refers to acute onset of flaccid paralysis of limbs of less than 4 weeks duration in a child under 15 years of age. The entity includes acute poliomyelitis, GBS, transverse myelitis and traumatic neuritis. With eradication of poliomyelitis from India, all conditions presenting with acute limpness or floppiness are not included under this entity under the acute flaccid paralysis (AFP) surveillance. For details, See Chapter 18 (Viral Infections).

GUILLAIN-BARRÉ SYNDROME

Postinfectious polyneuritis, acute inflammatory demyelinating polyradiculoneuropathy (AIDP), infective polyneuritis, infectious polyradiculitis

Definition

The term is applied to a nonspecific viral infection/inflammatory disorder of peripheral nerves and nerve roots characterized by symmetrical muscle weakness, sluggish or absent tendon reflexes, paresthesia or other sensory disturbances and autonomic dysfunction. Maximum cases are seen in the age group 5–12 years.

Etiopathogenesis

The condition has a definite relationship to diseases such as measles, chickenpox and rubella. Infectious mononucleosis (glandular fever), mumps, influenza and coxsackie or enteric cytopathic human orphan (ECHO) infections have

also been incriminated. What is important is that the polyneuritis usually starts after a substantial interval of about 10 days following the viral infection. Hence, the term **postinfectious** appears to be most appropriate.

The mechanism of causation too is not clear. It appears that breakdown of the nerve myelin occurs as an autoimmune process following the migration of the peripheral lymphocytes which have been sensitized to a protein component of the myelin. The myelin undergoes destruction as a result.

Clinical Features

- The earliest manifestation is muscle pain followed by weakness in the proximal as well as distal group of muscles
- Characteristically, muscle involvement is symmetrical in distribution and not in extent (Fig. 28.8)
- Muscle involvement first begins in the lower limbs and then spreads to the trunk, upper limbs and face
- Muscle tone is reduced, so are the tendon reflexes. Plantars are usually downgoing
- Involvement of the intercostal muscles may lead to respiratory difficulty
- Hypertension or urinary retention may result from involvement of the autonomic system
- There may be sensory symptoms, e.g. paresthesias
- Involvement of cranial nerves VIII, IX, X and XI may occur. The most frequently involved one is, however, facial nerve
- Infrequently, the disorder may present as ataxia
- GBS with involvement of cranial nerves and cerebellar signs is termed **Miller-Fisher variant**.

Diagnosis

- The CSF usually shows a characteristic cytoalbuminous dissociation toward the second week of illness. Often



Fig. 28.8: Guillain-Barré syndrome. The child started with flaccid paralysis of the lower limbs with some sensory loss. Paralysis ascended to involve respiratory muscles causing increasing respiratory distress warranting use of a ventilator.

the protein may be as high as 400–500 mg% although the cell count remains normal or only slightly raised. The so-called **cytoalbuminous dissociation** (also called **albuminocytologic dissociation**) in a child with acute or subacute polyneuropathy is considered pathognomonic (diagnostic) of GBS.

- Motor nerve conduction velocities and sensory conduction time are slow.
- Electromyography reveals acute denervation of muscle.
- Muscle and nerve biopsies, though not needed for diagnosis, show denervation atrophy and demyelination, degeneration and inflammation, respectively.

Differential Diagnosis

Differential diagnosis is from:

- Acute flaccid paralysis, i.e. poliomyelitis, traumatic myelitis and transverse myelitis.
- Polyneuritis following diphtheria, enteric fever, botulism, tick-bite paralysis.
- Other illnesses like polymyositis and cerebellar ataxia.

Treatment

Supportive treatment is more or less on the same lines as in poliomyelitis.

- Plasma exchange (plasmapheresis) or high-dose intravenous gamma globulins (IVIG), 1 g/kg/day for 2 days or 400 mg/kg/day for 5 days, is the treatment of choice at present. This treatment helps by removing the circulating immune complexes
- Severe illness with respiratory paralysis/failure requires management with assisted ventilation. Prevention of decubitus ulcers in case of flaccid tetraplegia and prevention/treatment of secondary bacterial infections are vital
- Chronic relapsing GBS needs repeated plasma exchange. Steroids, especially high-dose pulsed methylprednisolone by intravenous (IV) route, may be employed as less effective alternative modality.

Steroids, including high-dose pulsed methylprednisolone by IV route, though employed in the past, are no longer recommended.

Prognosis

Most cases (60–70%) usually show complete recovery within a few weeks to months. At times it may take as much as 2 years. Mortality (around 5%) is usually secondary to respiratory complications. Many subjects with chronic relapsing GBS end up with considerable residual disability in the form of foot drop, pes cavus, postural tremors and weakness of limbs and trunk.

PARAPLEGIA

Definition

The term, paraplegia, refers to paralysis of both lower limbs usually following diseases of spinal cord and, infrequently, intracranial lesions, peripheral nerve lesions or muscle diseases. When paralysis is incomplete, the weakness is partial. The term, paraparesis, is more appropriate in such a situation.

Box 28.5 Etiology of paraplegia**Spastic (Upper motor neuron type)**

- **Spinal cord compression:** Extradural, intradural or intramedullary primary tumors, secondaries, abscesses
- **Vascular:** AV malformations, telangiectasia, angiomas
- **Inflammatory:** Transverse myelitis from neuromyelitis optica, tuberculosis
- **Degenerative:** Familial spastic paraplegia
- **Demyelinating:** Postvaccinal (antirabic vaccine)
- **Congenital/hereditary:** CP, Friedreich ataxia
- **Toxic:** Lathyrism

Flaccid (Lower motor neuron type)

- **Spinal shock:** Initial manifestation following spinal trauma, inflammation, vascular or neoplastic insult
- **Inflammatory/postinflammatory:** Poliomyelitis, Guillain-Barré syndrome, polyneuritis
- **Muscle weakness:** Peroneal muscular atrophy, myasthenia gravis, muscular dystrophies
- **Miscellaneous:** Riley-Day syndrome, asymptomatic reflexia (Adie pupil), hysteria.

Abbreviations: AV, atrioventricular; CP, cerebral palsy.

Paraplegia may be acute or chronic, spastic or flaccid, and complete or incomplete. In **paraplegia in flexion**, there is complete involvement of the pyramidal tracts of the spinal cord. The tone in the lower limbs is more reduced in the flexors, thereby making them more flexed at knee and hip. A stimulation cause painful flexor spasm. In **paraplegia in extension**, the spinal cord lesion is incomplete. There is increase in tone of the extensors of the lower limbs. The term, **quadriplegia** or **tetraplegia**, implies involvement of all the four limbs. The term, **monoplegia**, refers to involvement of only one limb.

Etiopathogenesis

Box 28.5 provides etiologic classification depending on whether paraplegia is spastic or flaccid. Notable causes of

Box 28.6 Clinical features of paraplegia**Upper motor neuron lesion**

- Presence of exaggerated deep reflexes with clonus below the location of the spinal cord lesions
- Loss of power of a group of muscles
- Upgoing big toe (extensor plantar response)
- Upper motor type of bladder.

Lower motor neuron lesion

- Presence of muscle wasting/fasciculations
- Root pains
- Circumferential segmental hyperesthesia and exaggerated autonomic
- Absence of certain superficial or deep reflexes
- Autonomous bladder.

cortical paraplegia include CP, cortical venous thrombosis and spinocerebellar hereditary spastic paraplegia. More important among the spinal causes are transverse myelitis, epidural abscess, caries spine, GBS, poliomyelitis, trauma and herpes zoster.

Clinical Features

In addition to the manifestations of causative lesion the child shows following features depending on involvement of upper or lower motor neurons (Box 28.6).

Though initially the paraplegia may well be flaccid, in due course it becomes spastic from stimulation of pain fibers and the resultant painful flexor spasms.

Diagnosis

A detailed history and physical examination assist in arriving at the precise diagnosis of paraplegia and in determining the level of lesion. A spinal swelling/tenderness, dimple, tuft of hair or lipoma over the back should be specially looked for. Table 28.1 gives the useful information for localizing the causative lesion in paraplegia.

Table 28.1: Manifestations and signs helpful in localizing lesion in pediatric paraplegia

Observed symptoms and signs	Muscles involved	Level of lesion
Spastic paralysis of trunk and lower limb muscles; reflexes in lower limbs brisk	Flexors of wrists and fingers, muscles of the hand	C8, T1
Spastic paralysis of abdomen and lower limb muscles.	Intercostals, rectus abdominalis (both upper and lower), oblique abdominalis	T6
Spastic paraplegia; upper abdominals absent	Lower half of rectus abdominalis	T9, T10
Spastic paraplegia; lower abdominals absent	Lower fibers of oblique abdominalis and transversalis iliopsoas	T12 L1
Spastic paraplegia; knee jerk lost, ankle jerk present	Quadriceps, abductors of hip	L3, L4
All movements in lower limbs weak, except flexion of hip, adduction of thigh, extension of knee and dorsiflexion of foot; knee jerk, ankle jerk, plantars absent	Gluteals, calves, anterior tibials, peroneals, small muscles of foot	S1, S2
Anesthesia below folds of groin (including genitalia), bladder and rectal control lost; deep reflexes absent	Paralysis of lower limbs	Whole cauda equina
Sensory loss over front, lateral and posterior aspect of thighs, knee jerk and ankle jerk absent	Paralysis of gluteal, hamstrings and all muscles below knee	Upper sacral L5
Saddle-shaped area of anesthesia, urinary incontinence, fecal incontinence; no reflex in lower limb affected	No lower limb paralysis	Below S2
Anesthesia of anus and rectum	Paralysis of levator ani	S4, S5

Management

Specific

It depends on the etiologic diagnosis.

- **Acute myelitis** needs steroids in high doses either prednisolone as high as 5 mg/kg/day oral (O) or methylprednisolone pulse (IV) for 3 days.
- Naloxone, 5 mg/kg/day, is of value in reducing the ischemic damage.
- Anti-tuberculosis treatment (ATT) with steroids plus local treatment is needed in case of caries spine
- **Traumatic paraplegia** may well be an indication for a surgical intervention.
- **Paraplegia secondary to a spinal growth** too is an indication for a surgical intervention.

Supportive

- **Good nursing care** with attention to skin, bladder and bowel is mandatory. Frequent turning of the patient in the bed provided with foam mattress so that decubitus ulcers are prevented, is important.
- **Physiotherapy** involves emptying the urinary bladder by compression or catheterization so that it does not become distended, atonic, and even spastic with frequent but only incomplete reflex emptying. Inappropriate bladder drainage makes it quite susceptible to urinary tract infection (UTI), requiring specific therapy. First passive and later active physiotherapy helps to prevent contractures and deformities.

RHEUMATIC CHOREA

(Sydenham Chorea)

This major manifestation of burn-out rheumatic disease is discussed in Chapter 27 (Pediatric Cardiology).

INFANTILE TREMOR SYNDROME

See Chapter 48 (Miscellaneous and Unclassified Issues).

ATAXIA

Definition

The term, ataxia or incoordination, refers to the difficulty or inability to perform certain acts due to imperfect or absent coordination between different muscles or groups of muscles.

Types

Ataxia may be cerebellar or sensory due to involvement of posterior column.

In **cerebellar ataxia**, Romberg sign (failure to maintain standing attitude while standing on tiptoes and knees bent when the eyes are closed) is usually negative whereas cerebellar signs like nystagmus, dysarthria, hypotonia and pendular jerks may be positive. The child is unable to execute rapidly-repeated movements. On the contrary, his movements become slow, awkward and incomplete. This is called **adiadochokinesia**.

In **sensory ataxia** due to posterior column lesion, Romberg sign is positive and there may be other evidence of sensory loss.

Box 28.7 Causes of ataxia

- **Cerebellar acute:** Acute cerebellar ataxia, drug toxicity (piperazine, phenytoin), raised intracranial pressure, trauma, anoxia, seizures, hysteria, migraine, hypoglycemia, Guillain-Barre syndrome, cerebral abscess.
- **Chronic or subacute:** Space-occupying lesion (medulloblastoma, astrocytoma, tuberculoma, occult neuroblastoma), cerebral palsy, arrested hydrocephalus, congenital malformations (Arnold-Chiari or Dandy-Walker anomalies), degenerative diseases (Friedreich ataxia, ataxia telangiectasia, multiple sclerosis), metabolic disorders (abetalipoproteinemia, Hartnup disease, storage diseases), certain hereditary disorders (Refsum syndrome).
- **Sensory:** Juvenile tabes dorsalis, pernicious anemia complicated by subacute combined degeneration, polyneuropathies.

Etiology

Box 28.7 presents the list of causes of ataxia.

ACUTE CEREBELLAR ATAXIA

Acute cerebellar ataxia, usually occurring at 1–5 years of age, follows a viral infection such as chickenpox, poliovirus type I, influenza A and B, echo virus and coxsackie type B, or results from an autoimmune response to a variety of agents. The onset of ataxia is always acute. In 50% of the cases, however, a nonspecific infection precedes it by about 3 weeks or less.

- **Clinical features:** The most dominant feature of the clinical picture is the severe truncal ataxia resulting in rapid deterioration of gait.
- **Diagnosis:** Diagnosis is by exclusion of other causes of cerebellar ataxia. CSF is usually normal though a slight pleocytosis may occur in 25% of the cases. Late in the course of the disease, CSF proteins may be high.
- **Pleocytosis:** It is a self-limiting disorder; ataxia is clear fully in about 2 months in a large majority of the full-blown cases and in just a week or so in mild cases. No specific treatment is needed.

SPASMUS NUTANS

This disorder of unknown etiology is characterized by rhythmic jerking movements of head in the form of intermittent head nodding, usually in the lateral or horizontal direction, together with intermittent rapid pendular nystagmus. The movements disappear when the child concentrates or sleeps.

The manifestations are noticed from the age of 4–12 months; always disappear spontaneously by the age of 3–4 years. Inadequate lighting and absence of visual stimuli have been incriminated as the etiologic factors, but without sufficient evidence.

MENTAL RETARDATION

(Intellectual Disability)

Definition

Mental retardation is defined as subaverage intelligence, low learning capacity, poor maturation and inadequate social adjustment.

Box 28.8 Current classification of mental retardation

- **Borderline mental retardation (IQ 70–85):** Children who are vulnerable to educational difficulties which are usually sorted out with special help in regular classes.
- **Mild mental retardation (IQ 50–70):** Children needing at least some special class placement; some may attain 4th to 6th class reading levels.
- **Moderate mental retardation (IQ 35–50):** Children capable of attaining academic skills up to 2nd class; educational goals are targeted at gaining maximal self-care primarily.
- **Severe mental retardation (IQ 20–35):** Refers to children who can learn only minimal self-care and simple conversational skills; much supervision is a must.
- **Profound mental retardation (IQ under 20):** Children with minimal language development and only very minimal self-care skills; total supervision is a must.

Classification

Box 28.8 gives the current classification of mental retardation which is based on intelligence quotient (IQ).

$$IQ = \frac{\text{Mental age}}{\text{Chronological age}} \times 100$$

The old classification, expressing mental retardation in terms of idiot, imbecile and dull—which have taken derogatory meanings—is no longer employed.

It is customary to designate children with mild mental retardation as **educable** and moderate mental retardation as **trainable**. The severe and profound mental retardation is termed **custodial**. Nevertheless, some degree of education and training is possible even in the severe and profoundly retarded children.

Epidemiology

Prevalence of mental retardation (IQ under 70) in general population is nearly 3%. A vast majority of them (80–90%) is only mildly retarded; only 5% is with severe to profound impairment.

Etiology

Mental retardation may be as a result of prenatal, perinatal or postnatal causes (Box 28.9). Quite a proportion of children suffering from mental retardation may not fit into any of the known causes mentioned above. Equally noteworthy is the fact that, besides the etiologic factors (more exactly the potential contributory factors), there are at least four predisposing factors for mental retardation, namely.

- Poor socioeconomic status
- Low birthweight
- Advanced maternal age
- Consanguinity.

All these predisposing factors render a subject, prenatally, or postnatally, vulnerable to the etiologic or contributory influences. Genetic syndromes associated with mental retardation include Down syndrome, Edward syndrome, Fragile X syndrome, Klinefelter syndrome, phenylketonuria (PKU), tuberous sclerosis, neurofi-

Box 28.9 Etiology of mental retardation

- Prenatal
 - **Genetic:** Galactosemia, gargoylism, phenylketonuria, Niemann-Pick disease, Gaucher disease, microcephaly, craniosynostosis and congenital hydrocephalus
 - **Chromosomal:** Down syndrome, Turner syndrome, Klinefelter syndrome, Fragile X syndrome
 - **Maternal infections:** Rubella (Fig. 28.9), toxoplasmosis, cytomegalic inclusion disease, syphilis and chickenpox
 - **Maternal diseases:** Toxemias of pregnancy, lead poisoning, teratogenic agents, irradiation.
- Perinatal
 - Birth trauma, cerebral anoxia, hemorrhage, subdural hematoma
 - Prematurity, small-for-dates infant.
- Postnatal
 - **Infections:** Encephalitis, meningitis
 - **Trauma:** Head injury, subdural hematoma
 - **Encephalopathy:** Whooping cough, toxic. Kernicterus
 - **Cerebrovascular episodes:** Thrombosis of cerebral arteries and veins
 - **Endocrine:** Hypothyroidism
 - **Metabolic:** Hypoglycemia, hypocalcemia and profound electrolyte imbalance
 - **Cultural (postnatal experiential disruptions):** Poverty and family disorganization, faulty infant-caretaker interaction, parental psychopathology, parental drug abuse
 - Gross PEM in early infancy.

Abbreviation: PEM, protein energy malnutrition.



Fig. 28.9: Microcephaly with mental retardation. Cause is maternal rubella.

bromatosis, galactosemia, gargoylism, and Leisch-Nyhan syndrome. **Preventable mental retardation** embraces such causative/contributory conditions as are vulnerable to prevention (Box 28.10).

Clinical Features

- Failure to meet age-appropriate expectations such as delayed speech, language disabilities and delayed motor milestones, constitutes the hallmark of clinical manifestations.

Box 28.10 Preventable causes of mental retardation

- Congenital hypothyroidism (cretinism)
- Galactosemia
- PKU
- Kernicterus
- CNS infections (meningitis, cerebral malaria)
- Malnutrition including maternal malnutrition and IUGR
- LBW
- Consanguinity.

Abbreviations: PKU, phenylketonuria; CNS, central nervous system; IUGR, intrauterine growth restriction; LBW, low birth weight.

- Hyperactivity, poor memory, poor attention, poor concentration, distractibility, emotional instability, sleep problems, impulsiveness and awkward (clumsy) movements and seizures are usually present in some combinations.
- In certain conditions such as Down syndrome, primary microcephaly, mucopolysaccharidosis, congenital hypothyroidism, etc. specific physical features may clinch the diagnosis right at birth or during early infancy.
- Presence of dysmorphic facies and/or certain atypical features (Box 28.11).

Diagnosis

Clinical diagnosis is made from the pointers in the history and physical examination, including fundoscopy and developmental assessment. Eventually, IQ testing, confirming that intellectual functioning is more than 2 standard deviations (SD) below the mean for age, by an expert should be done.

Assessment of Mental Age

The commonly employed methods include:

- Stanford-Binet scale
- Wechsler scale
- Bhatia-scale

Box 28.11 Atypical features associated with mental retardation

- **Head:** Microcrania, macrocrania
- **Scalp hair:** Double whorl, white lock, sparseness, absence
- **Eyes:** Microphthalmia, slant, hyper- or hypotelorism, epicanthal fold, Brushfield spots, coloboma, nystagmus, abnormal position of pupil
- **Ears:** Low-set, simple or abnormal formation
- **Nose:** Flat depressed bridge, upturned nares, small size
- **Face:** Hypoplastic jaw(s), increased length of philtrum
- **Mouth:** V-shaped (inverted) upper lip, high-arched palate
- **Teeth:** Abnormal enamelogenesis or odontogenesis
- **Hands:** Short, stubby fingers, long, thin tapered fingers, broad thumb, clinodactyly, abnormal nails, transverse palmar crease, short 4th or 5th metacarpals, abnormal dermatoglyphics (say, distal triradius)
- **Feet:** Short, stubby toes, broad large big toes, overlap of toes, deep crease leading from angle of first and second toes, short 4th and 5th metatarsals, abnormal dermatoglyphics
- **External genitalia:** Large testicles, micropenis, ambiguous genitalia.

Box 28.12 Evaluation of mental age in children over 5 years of age

- **6 years:** Recognition of the family members and telling the details; counting 1–20.
- **7 years:** Telling completely the parts of the body—drawing a figure of man.
- **8 years:** Names the days of the week and months of the year.
- **9 years:** Does simple calculations such as involving coins.
- **10 years:** Does complete arithmetic calculations; solves a problem.

For children under 5 years, Denver or Gessel developmental system may be employed for rough estimate of the developmental age. Thereafter, mental age may be approximately evaluated as per Box 28.12.

Investigations

Over and above routine investigations, such special investigations as urine chromatography, urine tests for metabolic disorders, chromosomal studies, biopsies, serologic tests, hormonal or enzyme assays, etc. are needed depending on the case scenario. X-rays, CSF, ECG, angiography, CT scan, MRI, etc. are indicated in special situations only.

Differential Diagnosis

Differential diagnosis is from the so-called *pseudomental retardation* which may be secondary to:

- Psychiatric problems like autism
- Speech/hearing problems
- Deprivation (cultural, educational, environmental, emotional, or sensory in the form of deafness or blindness)
- Motor disability (paralysis, chronic myopathy).

Management

Multidisciplinary approach with a spotlight on specialized educational and therapeutic services forms the backbone of management of child with mental retardation.

- The family needs not only to be fully informed about the various aspects of child's disability but also wisely counseled and provided emotional support.
- The child must be provided with the routine basic healthcare, including immunization, growth monitoring and therapy of illness as and when need be.
- Management of common accompaniments of mental retardation like seizures, impaired vision and hearing, musculoskeletal disability, hyperactivity, squint, etc. is important.
- Central to all management is the warmth and appreciation of the caregiver rather than harsh criticism.

Today, thanks to welcome changes in social and political attitudes toward individuals with mental retardation over the recent decades, we no longer recommend placement of the mentally retarded in residential institutions (the so-called *institutionalization*). The trend now is to develop community-based service system, e.g. day-care centers, schools, integrated schools, vocational training centers,

518 sheltered farms and workshops, which coordinate services for both the child and his parents. The goal is to normalize the life of the child and his family rather than to pass the buck by putting the child away as was the practice in the past.

Prevention

The crux of all endeavors aimed at preventing mental retardation is promotion of healthy brain, intellectual development and provision of a nurturing and growth-promoting environment. The following measures may be of special help:

- Emphasis on the overall welfare of the girl child, the future mother, ensuring that her nutritional status is good and that she is safeguarded against teenage pregnancy as also that she has been adequately vaccinated against rubella.
- Avoidance of consanguineous marriages. Risk of metabolic disorders of recessive inheritance appearing in homozygous form is high in such unions.
- Mothers beyond 35 years of age need to be informed about the enhanced risk of birth of a child with Down syndrome.
- During labor, birth trauma and neonatal asphyxia must be prevented through good obstetric care.
- After birth, such causes of mental retardation as hyperbilirubinemia, meningitis, congenital hypothyroidism, galactosemia and phenylketonuria must be promptly identified and managed adequately
- Prevention and management of low birth weight infants as also malnutrition in infancy and early childhood.

DOWN SYNDROME

(Mongolism)

Down syndrome is perhaps the most common among the well-recognized causes of mental retardation. Incidence in India is 2.2 per 1,000 live births which is higher than the average overall figure of 1 in 600 for all races.

Types

Three cytogenetic types are known:

1. **Trisomy 21** (95% cases) which results from the presence of an extra chromosome 21. Such a mongol has 47 chromosomes instead of the normal 46. Also called **Trisomy G**, it is associated with advancing maternal age. A mongol is generally either first born or an exhaustion product, i.e. last of a series of pregnancies.
2. **Translocation of chromosome 21** with chromosome 13, 14 or 15 (4% cases). In this type the total number remains the normal 46 though one chromosome is large and atypical.
3. **Mosacism may occur** occasionally (1% cases).

Clinical Features

Clinical picture is characteristic, having striking resemblance to Mongolian races like Chinese, Tibetans,

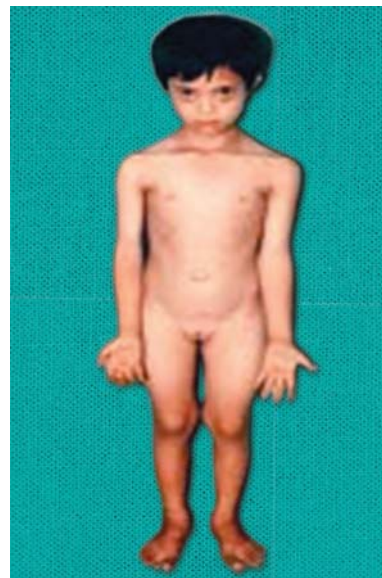


Fig. 28.10: Profile of a child with Down syndrome.

Japanese, etc. as far as facial appearance is concerned (Figs 28.10 and 28.11). A Down syndrome child is often described as a **cheerful idiot**—a derogatory expression that should be discouraged. Unlike a cretin, he is affectionate, friendly, fond of music and has grossly delayed milestones, both physical and mental. The maximum mental age is seldom beyond 8 years. Average IQ is about 40. Head is microcephalic with flattening of the occiput.

- **Facial features** include eyes having upward, slant*, epicanthal folds (generally at the inner angles) and occasionally Brushfields spots (small whitish spots near the periphery of the iris). Incidence of late-onset cataract is high. Tongue is protruded from the small buccal cavity and may be furrowed (scrotal tongue).
- **Nose** is short and its bridge flat. This together with epicanthal folds, gives an impression of increased distance between the eyes though interpupillary



Fig. 28.11: Down syndrome. Note the classical facial features in an infant.

* Mongoloid slant may also be seen in Laurence-Moon-Biedl syndrome. Its opposite, "antimongoloid slant" is usually encountered in Apert syndrome, Treacher-Collins syndrome, cerebral gigantism and de Lange syndrome.

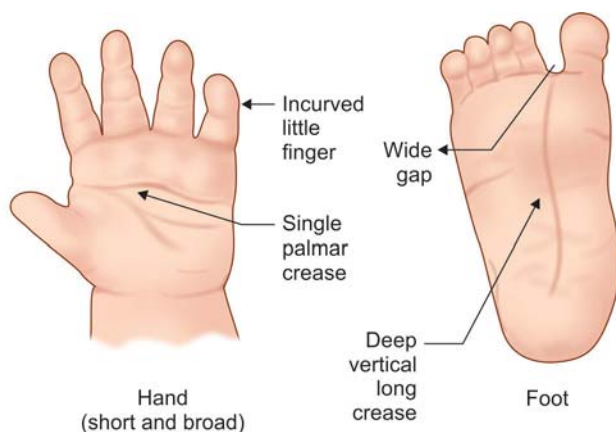


Fig. 28.12: Hand and sole of foot in Down syndrome.

distance remains normal (pseudohypertelorism). Ears are low-set* and often deformed; ear lobes may be absent or small. High-arched palate and malocclusion of the teeth may be present.

- **Neck** is short and broad. Often the head seems to be almost resting on trunk. Hairline is usually low.
- **Feet** show wide gap between the big and second toes and, at times, a deep crease starting between them and extending on the sole (Fig. 28.12).
- **Hands** are short and broad; little finger is short and incurved due to rudimentary middle phalanx. The normal 3 major creases may be replaced by a single transverse line called Simian crease (Fig 28.13).
- **Generalized hypotonia** is usually present. Mongolism should be considered in the differential diagnosis of the so-called floppy baby syndrome. As the child grows, hypotonia gradually diminishes. These children are highly susceptible to **recurrent respiratory infections** (Box 28.13). Poor development of the paranasal sinuses is responsible for recurrent upper airway infection.



Fig. 28.13: Simian (single palmar) crease in Down syndrome.

* A low-set ear lies below an imaginary line joining the lateral angle of the eye to the posterior occipital protuberance.

Box 28.13 Diseases showing higher incidence in Down syndrome

- Recurrent respiratory infections
- Coronary heart disease (CHD)
- Intestinal obstruction—duodenal atresia
- Hirschsprung disease
- Celiac disease
- Leukemias.

- **Associated congenital heart disease** (usually atrio-ventricular canal, ventricular septal defect {VSD} or atrial septal defect {ASD}—sometime tetralogy of Fallot {TOF}) is a common finding.

Moreover, they are 10 times more **prone to development of leukemia** than the normal population. Newborns with mongolism are more likely to develop **intestinal obstruction** due to duodenal atresia. Likewise, **Hirschsprung disease** occurs more often in them than in others. Around 10% cases of Down syndrome have biopsy-proven celiac disease.

Diagnosis

Clinical

Clinical picture is invariably so characteristic that the diagnosis is apparent. The difference between Down syndrome and congenital hypothyroidism are presented in Table 28.2. Also, See Chapter 39 (Pediatric Endocrinology). The clinical diagnosis may be confirmed by chromosomal studies.

Table 28.2: Down syndrome versus cretinism

Down syndrome	Congenital hypothyroidism
Cheerful	Repulsive
Active	Lethargic
Microcephaly with flattening of occiput	Generally absent
Fine tender skin	Rough skin
Upward slant of eyes	Absent
Epicanthal fold	Absent
Protruding, furrowed but normal-sized tongue	Large protruding tongue
Simian crease	Absent
Higher incidence of congenital heart disease, Hirschsprung disease, duodenal atresia and leukemia	No such predisposition
No definitive treatment available as it is of chromosomal etiology*	Replacement therapy available; it is a state of hypothyroidism
Maximum IQ attained, despite the best of efforts, is that of an 8-year-old	With adequate replacement therapy, started in first few months of life, IQ of 90 may be achieved

* Administration of 5-hydroxytryptophan is reported to revert the hypotonia.

520 Radiologic Findings

- Only 11 ribs
- Two to three ossification centers of manubrium
- Hypoplasia of base of skull, facial bones and middle phalanx of fifth finger
- Accessory epiphysis at base of second metacarpal
- Coxa valga
- **Bony pelvis:** Iliac are broad and flared; acetabular and iliac angles are reduced.

Dermatologic Findings

- Distal palmar axial triradius or large angle, hypothenar patterns, distal loop in the third interdigital area.
- Predominance of ulnar loops on the digits and radial loops on 4th and 5th fingers.
- Hallucal arch tibial pattern in the feet.
- Marked crease between great and second toes.

Management

The cornerstone of management of Down syndrome is to help the child to make the best of his limited abilities.

- **Parental counseling and occupational training:** These are helpful in many such patients for not only to take care of their person but also to carry occupations not requiring much sophistication.
- **Institutionalization:** The consensus is against early institutionalization. The useful impact of institution-alization for older child is well-recognized.
- **Symptomatic treatment,** as and when indicated, must be given. Recurrent respiratory infections are common. Antibiotics, if indicated, may be needed to control such an infection.

Box 28.14 gives the anticipated risk of another child with Down syndrome.

Box 28.14

Parental counseling: How risky will it be to have another child?

- **Child has trisomy 21, parents have normal karyotypes:** The risk is only slightly greater than for parents in the general population (1 to 2%).
- **Trisomy child, one parent mosaic:** The risk will depend upon the degree of gonadal mosaicism of the affected. A rough estimate will be half of the proportion of abnormal cells in fibroblast cultures of the cells obtained from the parent.
- **Child has 14/21 (D/G) translocation, parents have normal karyotype:** The risks are unknown but should be considered slightly increased.
- **Child has 14/21 (D/C) translocation carrier:** Two possible situations may arise. Firstly, when the mother is a carrier, about 15% of the children may be affected, one-third may be carriers and the remainder completely normal. Secondly, when the father is a carrier, there is 3–5% chance of having another affected child and half of the apparently unaffected children may be carriers.
- **Child has a 21/22 (G/G) translocation:** If both the parents have normal karyotype, the prognosis is roughly the same as under "A" although there is some evidence that advancing paternal age may increase the risk slightly. If, on the other hand, only one parent carries the translocation, the risk is 100% in case of an isochromosome of 21 (21/21) and same as under "D" in case of a 21/22 translocation.

AUTISM SPECTRUM DISORDER

Autism spectrum disorder is characterized by a qualitative impairment in verbal and nonverbal communication, in imaginative activity and in reciprocal social interaction. Incidence of low intelligence, epilepsy, self-injurious behavior and fragile X syndrome (in families) is high. For details, See Chapter 6 (Developmental, Behavioral and Psychiatric Disorders).

CEREBRAL PALSY (LITTLE DISEASE)*

Definition

Cerebral palsy is a form of chronic motor disability which results from damage to the growing brain before or during birth, or in postnatal period. Though grammatically incorrect, it has been dubbed as **nonprogressive, noncurable** and **nonfatal** by John Little, who first described it, to highlight its characteristics. CP is the most common cause of crippling in children.

Though mental retardation is associated in about 25–50% cases of CP, it is, by no means, an essential feature of the clinical picture. The other handicaps that the patient may have are epilepsy, orthopedic deformities, partial or complete deafness and blindness, psychologic disturbances, etc. (Fig. 28.14).

According to conservative estimates, prevalence rate of CP is in the vicinity of 4 per 1,000 live births. Since mild cases are likely to be missed in surveys, the prevalence of CP may well be higher than this estimate.

Etiology

It is more or less the same as in case of mental retardation with the following differences:



Fig. 28.14: Cerebral palsy. Note the typical posture epidemiology.

* After the name of William John Little, an orthopedic surgeon who first described it in 1862. Paradoxically, known for his works in childhood disabilities, he himself suffered from post-polio disability.

- Genetic and chromosomal factors do not operate here.
- Of the postnatal factors, hypothyroidism cultural influences and protein-energy malnutrition have nothing to do in the etiology of CP.

Cerebral anoxia, often accompanied by intraventricular and subependymal hemorrhages followed by physical birth trauma to the brain, kernicterus and congenital malformations of brain was believed to account for a large chunk of cases of CP.

Recently, convincing evidence has collected to show that birth asphyxia, earlier believed to be a leading cause of CP, is, in fact an uncommon etiologic factor in this entity. Current thinking is that roots of pathogenesis of CP may well be in the developmental biology.

Pathology

In milder CP, brain grossly appears normal but is underweight and has only sparse subcortical white matter and sparse nerve fibers. The findings in severe CP include widespread cerebral atrophy, cavity formation in subcortical white matter, atrophy of basal ganglia and porencephalitis.

Clinical Features

The following classifications are useful:

- Classification based on motor deficit and distribution of handicap
 - Spastic CP (pyramidal CP)
 - Quadriplegia
 - Paraplegia
 - Hemiplegia
 - Monoplegia.
 - Extrapyramidal CP
 - Choreoathetosis
 - Dystonia.
 - Atonic CP (Cerebellar CP)
 - Atonic diplegia
 - Congenital cerebellar ataxia.
 - Mixed CP
- Classification based on patient's status about functional capacity
 - **Class I:** No practical limitation of activity.
 - **Class II:** Slight to moderate limitation of activity.
 - **Class III:** Moderate to gross limitation of activity.
 - **Class IV:** Inability to carry on any useful physical activity.
- Classification based on patient's status about therapeutic needs
 - **Class I:** Not requiring any treatment.
 - **Class II:** Requiring minimal bracing and minimal therapy.
 - **Class III:** Requiring bracing and services of a CP team.
 - **Class IV:** Requiring long-term institutionalization and treatment.

Spastic CP is the type most frequently encountered in clinical practice. The classical form consists of spasticity of

both upper as well as lower limbs, legs being more severely affected than the arms (diplegia). In some cases, the picture may be that of hemiplegia, monoplegia or triplegia. **521**

Besides spasticity, deep tendon reflexes are brisk and ankle clonus may be positive. Also, plantars may be extensor. Sudden lifting of the child may produce visible adductor spasm and even crossing of the legs, the so-called **scissoring**, which is characteristic of CP.

As the child grows in age, spasticity and rigidity become more pronounced with development of abnormal postures and contractures, especially at heels, hips and elbow. Bilateral spasticity may lead to pseudobulbar palsy and resultant swallowing difficulties and excessive drooling. Cerebral palsy of this type can be diagnosed fairly early in infancy. Delay in attaining motor milestones and persistence of Moro, grasp, tonic neck and other primitive reflexes after the age of 3 months should arouse suspicion (Fig. 28.15). Early markers of CP are listed in Box 28.15.

Handicaps/Comorbidity

On top of disability from CP per se, a child with CP may have quite a few associated handicaps as shown in Box 28.16.

Diagnosis

Cerebral palsy must be considered in every child who fails to keep pace in attainment of milestones with the range of expected for the age. The diagnosis becomes more likely if there is evidence of abnormalities of posture, involuntary movements and neurologic deficit. A detailed history and physical examination with special reference to neurological and developmental status, language and learning disability, hearing and visual function evaluation, and psychometric and sensory deficit is vital.

Attempts must be made to rule out muscular dystrophy, degenerative disease, or spinal cord tumor. In order to localize the site and extent of the structural lesions or accompanied congenital malformations, EEG and CT scan may be done.

Treatment

The major aim of treatment in CP is to achieve maximum possible functional ability and skill in keeping with his developmental age. This is primarily achieved through physiotherapy, surgical corrections and occupational therapy.

Pharmacotherapy

- **Spasticity:** Diazepam, dantrolene sodium or baclofen
- **Hypotonia:** Strychnine
- **Athetosis:** Chlordiazepoxide or levodopa
- **Dystonia:** Carbamazepine or trihexyphenidyl (an antiparkinsonian agent)
- **Epilepsy:** Anticonvulsants.

Physiotherapy

This forms the cornerstone of management of CP. The subject is trained in relaxing the spastic muscles,

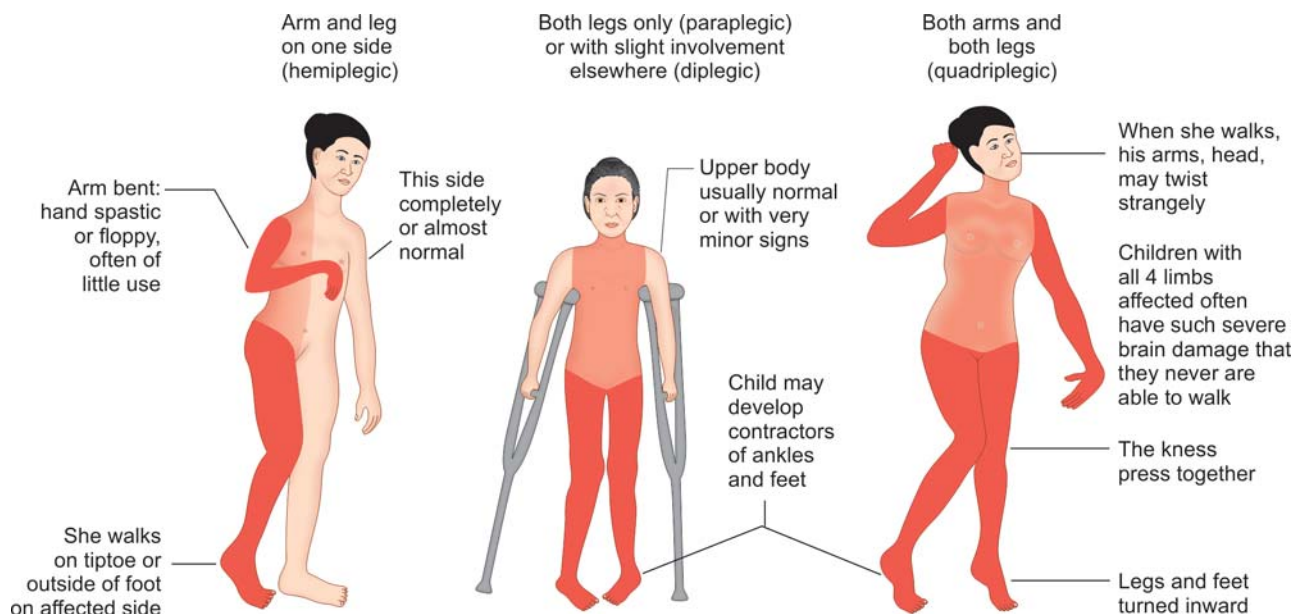


Fig. 28.15: Three most frequently seen patterns of cerebral palsy.

Box 28.15 Early markers of cerebral palsy

- Bilirubin encephalopathy
- Hypoxic-ischemic encephalopathy (HIE)
- Persistent Moro, tonic neck and other primitive reflexes after the age of 3 months.

Box 28.16 Common associations/handicaps (comorbidity in CP)

CNS

- Variable degree of mental retardation
- Behavioral problems
- Seizures

Ears

- Deafness (partial or complete)
- Receptive auditory aphasia

Eyes

- Squint
- ROP
- Cataract
- Coloboma
- Refractive errors
- Perceptual errors
- Blindness (partial or complete)

Speech

- Aphasia
- Dyslalia
- Dysarthria

Sensory

- Spatial disorientation
- Astereognosis

GIT

- Constipation
- Incontinence

Teeth

Malocclusion, caries

Miscellaneous

- Feeding difficulties
- Drooling
- Recurrent infections.

Abbreviations: GIT, gastrointestinal tract; CNS, Central nervous system; CP, cerebral palsy; ROP, retinopathy of prematurity.

encouraged to do active exercise to establish movement pattern and taught rhythmic contractions and relaxation of muscles. For assisting them to stand and walk, walking calipers are prescribed. In order to maintain the proper sleep posture (knee, foot and hand), night splints are used.

Occupational Therapy

This involves the positive application of certain repetitive movements of legs, hands and fingers to relax the spastic muscles. The subjects are also trained for some occupation when they grow up so that they turn out to be economically self-sufficient.

Surgical/Orthopedic Therapy

In the past, this was targeted at just correcting the deformities and stabilizing the joints.

Recently, gratifying results have been obtained by the procedure, **selective posterior rhizotomy**, in children with spastic CP involving primarily the lower limbs. In this surgical procedure, posterior rootlets of the cauda equina are stimulated electrically whereas abnormal ones are sectioned. In properly selected cases (reasonable cognitive status, good functional upper limbs, spasticity limited to lower limbs), the spasticity subsides virtually right on the operation table. Eventually, significant gain in milestones to the extent of walking can be expected. Nonetheless, rehabilitative therapy needs to be continued to compliment the positive outcome of the surgery and obtain the best results.

Finally, management of CP is teamwork, requiring coordination between the physicians from various specialties, surgeons, physical and occupational therapists, speech therapist, social worker, educator, development psychologist, parents and the child.

Voluntary organizations such as the Spastic Society of India, launched in 1972, and Indian Family of CP, launched in 1993, to serve the interests of the CP-affected children, need to be encouraged.

Prevention

Better obstetric, perinatal and neonatal care prevents birth trauma, birth asphyxia and kernicterus. Logically, it should cut down incidence of CP. However, it has recently been suggested that future developments targeted at enhancing perinatal care may have only marginal effect on the prevalence of CP as has been the case in prosperous countries. It may be worth-while to direct CP-related research to the area of developmental biology as well. Early and prompt detection of CP cases and adequate planning for management may help indirectly by reducing

residual neurological, psychosocial, and other handicaps, and making child's life comfortable.

MENINGITIS

Meningitis refers to the inflammation of the meninges overlying the brain and the spinal cord.* It is one of the most dreadful emergencies met within pediatric practice. The fatality rate is high. Two types are generally recognized.

1. **Pyogenic or bacterial:** *Hemophilus influenzae*, pneumococcal, meningococcal, staphylococcal, streptococcal and *Escherichia coli* infection.
2. **Aseptic:** Tuberculous, viral, fungal and protozoal (toxoplasmosis, amebic).

BACTERIAL MENINGITIS

Bacterial meningitis accounts for around 5% of the pediatric admissions in our country. It results from either primary infection of the meninges or spread from a nearby pyogenic focus. At times, metastatic spread from a distant focus also causes this disease. In our country, *Hemophilus influenzae* and *Pneumococcus* are** the leading causative agents. *Meningococcus*, *Staphylococcus* and *Streptococcus* are less common. *Escherichia coli* is infrequent indeed, except in neonatal meningitis. *Hemophilus influenzae*, in particular, affects mostly the infants and young children (Box 28.17).

Clinical Features

As a rule, the onset is sudden with high fever, vomiting, restlessness, irritability, headache and often convulsions. In newborns and small infants, pyogenic meningitis may have insidious onset with meagre symptoms like refusal to take feed, fever and irritability. Some may have convulsions. These, especially in the presence of bulging anterior fontanel, should arouse suspicion of meningitis.

Physical examination may reveal neck stiffness, and positive Kernig and Brudzinski signs. Cranial nerve palsies and papilledema are present in some cases. Hemiplegia may be noticed in a few cases who report late to the doctor.

Meningococcal meningitis is characterized by the presence of a generalized purpuric rash*** which is only

infrequently seen in dark-skinned children. Meningococemia may, in certain cases, dominate the clinical picture of meningitis. Such cases become rapidly comatose and have toxemia, cyanosis and purple mottling of the skin. This is called Waterhouse-Friderichsen syndrome.

Diagnosis

Lumbar puncture is a **must** in any child in whom meningitis is suspected. CSF is generally under increased pressure and frankly turbid or little opalescent. Cell count is greatly increased, a large proportion of these being polymorphs. CSF proteins are greatly increased. But, sugar is considerably reduced, invariably below 30 and often as low as 10 to 20 mg%. CSF culture should be done for identifying the causative organisms and their antibiotic sensitivity, provided such facilities are available.

Nitroblue tetrazolium (NBT) test is a useful adjunct to differentiate it from tuberculous meningitis; so is countercurrent immunoelectrophoresis.

Treatment

Antibiotic Therapy

- **Empirical:** Initial treatment of choice is empirical employing a third generation cephalosporin, ceftriaxone or cefotaxime (IV). Alternative choice is ampicillin, given intravenously in a dose of 100–400 mg/kg/day as such or in combination with chloramphenicol. The low dose of ampicillin is only for newborns under 7 days of age. In them it should be combined with an aminoglycoside (say, gentamicin or amikacin).

If the patient is hypersensitive to penicillin, ampicillin should not be given. Chloramphenicol, 50–100 mg/kg/day, is the next best agent. In a newborn, either it should be avoided or given in a low dose, i.e. 25 mg/kg/day, because of the risk of serious toxicity (gray baby syndrome).

Combination of chloramphenicol and penicillin continues to find favor with some clinicians.

- **Specific:** After availability of culture and sensitivity report, suitable change in antibiotic therapy may be made as per Box 28.18 provided that response to empirical therapy is unsatisfactory.

In case clinical response to therapy is satisfactory, antibiotic therapy may be stopped without a second LP. In most cases, duration of therapy is 10–14 days. *Pseudomonas* and other Gram-negative meningitis may need a longer course. Intrathecal administration of antibiotics, particularly initially, may be considered in neonates and patients with advanced disease. Rising ICP may be controlled by IV mannitol.

Corticosteroids

A short course of steroids (dexamethasone, 0.15 mg/kg/dose IV every 6 hourly × 3 days; the first dose greater

Box 28.17 Agewise etiology of pyogenic meningitis

Under 2 months

- Gram-negative organisms, especially, *E. coli*
- Group B beta-Streptococcus hemolyticus
- *Listeria monocytogenes*

2 months to 6 years

- *Hemophilus influenzae*
- *Pneumococcus*
- *Neisseria meningitidis*

Beyond 6 years

- *Pneumococcus*
- *Neisseria meningitidis*.

* Strictly speaking, the term meningitis is a misnomer since it is virtually impossible that inflammation is limited to the meninges only. Meningoencephalitis is a better nomenclature.

** Caused epidemic of meningococcal meningitis in Delhi in early, 1985.

*** Such a rash may also be seen in pneumococcal meningitis, influenza (type B) and some other viral infections.

Box 28.18**Recommended intravenous antibiotics in acute bacterial meningitis based on culture and sensitivity report*****Pneumococcal meningitis***

- **First choice:** Penicillin G
- **Alternative:** Cefotaxime or ceftriaxone

Meningococcal meningitis

- **First choice:** Penicillin G
- **Alternative:** Cefotaxime or ceftriaxone

Hemophilus influenza meningitis

- **First choice:** Ceftriaxone or cefotaxime
- **Alternative:** Ampicillin + Chloramphenicol

Staphylococcal meningitis

- Penicillin G in case of penicillin-sensitive pathogens
- Vancomycin in case of penicillin-resistant pathogens.
- *Listeria meningitis*
- Ampicillin + Amikacin, netilmicin or gentamicin.

Pseudomonas meningitis

- **First choice:** Ceftazidime + Amikacin, netilmicin or gentamicin
- **Second choice:** Piperacillin or ticarcillin or Meropenem or Cefepime.

than 15 minutes before starting antibiotics), especially in *Hemophilus influenzae* meningitis, is recommended in postneonatal cases. Its benefits include reduction in frequency of neurological complications such as deafness (sensorineural), internal hydrocephalus and behavioral problems.

Controlling Seizures

Anticonvulsant agents such as IV diazepam and/or phenytoin are usually needed to control seizures.

Controlling Raised Intracranial Pressure

Mannitol, 0.5 g/kg of 20% solution, is given IV stat and then every 4–6 hourly. Total administration must not exceed 6 doses.

Controlling Blood Pressure

Dopamine or dobutamine as vasopressors are useful in controlling associated hypotension.

Supportive Measures

- Maintenance of hydration, nutrition (IV drip is almost indispensable for first few days), vitamin supplements and good nursing care.
- Syndrome of inappropriate secretion of antidiuretic hormone (ADH) syndrome of inappropriate antidiuretic hormone (SIADH) warrants cutting down of maintenance fluids by one-third.
- Good nursing care.

Complications

The complications include:

- Subdural effusion/empyema
- Brain abscess
- Hydrocephalus
- Deafness, blindness, ocular paralysis.

Prognosis

The outlook has now considerably improved with the availability of modern antibiotics. Most of the mortality is confined to neonatal meningitis.

Sequelae

The sequelae include mental retardation, epilepsy, speech problems, hearing loss (due to labyrinthitis, or direct inflammation of auditory nerve), visual impairment, varying pareses, hydrocephalus, diabetes insipidus, obesity and precocious puberty.

NEUROTUBERCULOSIS**(Central Nervous System Tuberculosis)**

Four major forms of neurotuberculosis are:

1. Tuberculous meningitis
2. Tuberculous encephalopathy
3. Tuberculoma
4. Tuberculosis of the spine.

Tuberculous meningitis (TBM) is the most common and the most serious form of CNS tuberculosis. Around 12–20% of children with tuberculosis have TBM.

Epidemiology

The incidence is particularly high in dark races, the Negroes being the toppers. The maximum risk of TBM is 3–6 months after the primary infection and much less after a year. Hence, highest incidence is recorded in the preschoolers, the peak being 6–24 months of age.

TBM and miliary tuberculosis do not always coexist though TBM is always the result of hematogenous spread from primary lesion(s) elsewhere. This lesion may be neither clinically manifest nor detectable.

History of an illness like measles may precede the onset of TBM. Bacillus Calmette-Guérin vaccination brings down the incidence and severity but does not prevent TBM.

Etiopathogenesis

In a large majority of the cases, TBM is due to human *Mycobacterium tuberculosis* and is always a secondary lesion with the primary usually in the lung. The involvement of meninges is believed to be from the discharge of the bacilli in the CSF by the small tuberculoma in the cortex of spinal cord or tuberculous lesion of the vertebrae. At times, tuberculosis of the choroid plexus may be the site for the spread of infection to the meninges. Small tubercles are scattered over the convexity of the brain or periventricular area.

Clinical Features

In a classical case, TBM has insidious onset. Acute onset is frequent in infancy, however. The course of illness may be divided into 3 stages—prodromal, transitional or terminal.

First or Prodromal Stage

Here the symptoms are vague and include change in disposition and temperament (apathy or irritability), drowsiness, mild fever, convulsions, anorexia, vomiting, constipation and headache.

Second or Transitional Stage

During this stage, manifestations of raised intracranial tension and meningeal irritation appear. Child becomes



Fig. 28.16: Tuberculous meningitis. Facial palsy of upper motor neuron type.

progressively drowsy and even unconscious. Headache, vomiting and feverishness become more aggravated. Neck rigidity and Kerning sign become positive. Plantar reflexes may become extensor. Ankle and patellar clonus may be elicitable. Abdominal reflexes, on the contrary, disappear. Hypertonia is usually present, so are the seizures. In small infants anterior fontanel may be bulging. Cranial nerves involved are 3rd, 4th, 6th and 7th (Fig. 28.16). Ocular paralysis, strabismus, nystagmus and contracted pupils are common. Also, there may be papilledema. Choroid tubercles along the blood vessels of choroid plexus may be seen in a small proportion of the cases.

Third or Terminal Stage

This is the stage of paralysis and coma (Fig. 28.17). Although there may be short periods of wakefulness. Signs of meningeal irritation are no longer prominent. Pupils are dilated and fixed. Clonic spasms of limbs, irregular respiration, irregular pulse (slow or rapid), rising fever and widespread paralysis are present. If treatment is delayed or inadequate, hydrocephalus invariably develops in infants and small children.

Roughly, each of the stages described above lasts for about a week or so. There may be considerable

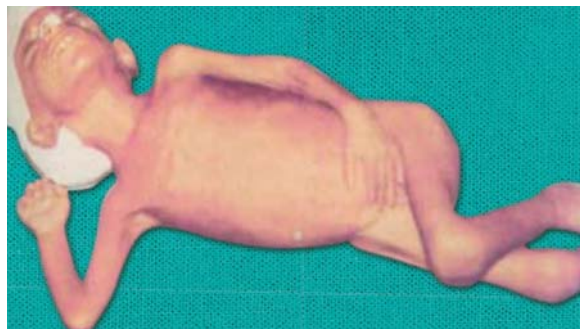


Fig. 28.17: Tuberculous meningitis. Note features of stage 3 plus gross malnutrition.

overlap of the three stages. With treatment, there may be prolongation or even absence of one of the stages.

Remember also that, TBM may have odd presentation simulating typhoid, brain tumor, status epilepticus, poliomyelitis, spinal cord compression, congenital hydrocephalus, acute abdomen, intracranial injury, gastritis, or bronchopneumonia. In grossly malnourished children, TBM may present in the form of irregular but persistent pyrexia without significant manifestations of meningeal involvement. Rarely, a case of TBM may remain conscious throughout illness. Coexistence of both TBM and pyogenic meningitis in the same patient has infrequently been observed by us as well as by others. The same is true about TBM and typhoid.

Diagnosis

Early diagnosis is of utmost importance for full recovery as well as prevention of complications and/or sequelae.

- **Suspicion:** A high index of clinical suspicion, especially in areas where tuberculosis is common, goes a long way in detecting the cases at early stages.
- **Mantoux test:** Though a positive tuberculin test (greater than 10 mm in duration) is helpful, a negative test does not exclude TBM See Chapter 26 (Pediatric Pulmonology).
- **Lumbar puncture:** Cerebrospinal fluid provides most dependable information. It gushes out under high pressure and is clear or, occasionally, slightly turbid. When it is kept in a test tube for 12 hours, a cobweb is formed. Microscopic examination shows an increase in cell count from 10–500/mm³ with predominance of lymphocytes. In some cases with acute onset, especially in infants, CSF in early stage of TBM may show relative increase in polymorphonuclear cells. Biochemical examination shows increase in proteins whereas sugar and chlorides are reduced. Absolute confirmation of the diagnosis is obtained by demonstration of the tuberculous bacilli in the CSF smear, by culture, or by guinea-pig inoculation.
- Supportive investigations include chest X-rays, skull X-ray, CT scan (Fig. 28.18) and erythrocyte sedimentation rate (ESR).
 - Sputum or gastric lavage may be done.
 - A lymph node biopsy, liver biopsy or bone marrow may be helpful in cases of diagnostic dilemma.
 - Biochemical markers that yield quick results include bromide partition test, adenosine deaminase and tuberculostearic acid.
- **Serodiagnosis:** It consists in detecting antigens, antibodies or immune complexes in CSF or, at times, in serum usually by enzyme-linked immunosorbent assay (ELISA).
- Molecular diagnosis is by polymerase chain reaction (PCR) or deoxyribonucleic acid (DNA) probing method, though very reliable, is very expensive and not usually required.



Fig. 28.18: Computed tomography scan demonstrating grossly dilated ventricular system in tuberculous meningitis (TBM).

Differential Diagnosis

- Bacterial meningitis
- Meningoencephalitis: Viral, amebic
- Encephalopathy: Typhoid
- Brain abscess
- Intracranial space-occupying lesions (ICSOL): Brain tumors
- Chronic subdural hematoma.

Treatment

Anti-tuberculosis Treatment

According to the current national and Indian Academy of Pediatrics (IAP) recommendations, chemotherapy consists of 2HRZE/10HRE with prednisolone as per Box 28.19.

Corticosteroids

In order to reduce cerebral edema and risk of such complications as arachnoiditis, fibrosis, adhesions and spinal block, steroids are strongly recommended.

To begin with, IV dexamethasone, 0.15 mg/kg every 6 hourly should be given until raised ICP is controlled. Thereafter, prednisolone 1–2 mg/kg/day for 8 weeks (first 6 weeks, full dose; last two weeks, tapering) is recommended.

Reduction of Cerebral Edema

The additional measures to reduce cerebral edema include administration of 20% mannitol, 100–200 mL (IV)

Box 28.19

Anti-tuberculosis treatment in tuberculous meningitis

- Isoniazid 5 mg/kg/day 12 months
- Rifampicin 10 mg/kg/day 12 months
- Pyrazinamide 25 mg/kg/day 2 months
- Ethambutol 20 mg/kg/day 2 months
- Streptomycin 20 mg/kg/day 2 months.

twice daily for 5–7 days, glycerol 10%, 1.5–2 g/kg (O or IV), or hypertonic glucose, fructose or urea.

Shunt is indicated in case of hydrocephalus, provided that CSF protein does not exceed 100 mg%. High CSF protein is likely to block the shunt.

Controlling Seizures

The child should receive an anticonvulsant like diazepam, phenobarbital, and phenytoin to control convulsions.

Supportive Measures

- Good nursing care
- Maintenance of fluid and electrolyte balance and nutrition
- Treatment of evolving complications like decerebration, hydrocephalus.

Prognosis

Without treatment, TBM, almost always ends fatally. Even with treatment, mortality is high. Mortality figures are relatively higher in infants, in highly advanced cases (stage 3), development of seizures, delay in starting proper treatment and in malnourished children.

In developing regions, relapses do occasionally occur in those cases of TBM who receive inadequate antituberculous therapy.

Sequelae

The common sequelae seen in survivors from third stage are listed in Box 28.20.

TUBERCULOUS ENCEPHALOPATHY

Definition

Tuberculous encephalopathy is defined as CNS tuberculosis in the absence of meningeal signs and nearly normal CSF.

Clinical Features

- Onset may be acute, subacute or vaguely chronic
- The manifestations are mild, moderate or severe, depending upon the severity of pathologic lesions of the brain cells
- Alteration in sensorium in the form of drowsiness, semiconsciousness and even coma is invariably present
- Convulsions are generally there
- Despite diffuse cerebral signs, meningeal signs are remarkable by their absence

Box 28.20

Common sequelae of tuberculous meningitis

- Mental retardation
- Epilepsy
- Acquired hydrocephalus (Fig. 28.19)
- Cranial nerve paralysis
- Hemiplegia, quadriplegia, monoplegia
- Movement disorder—tremors, ataxia, spasticity
- Midline cerebellar syndromes
- Endocrinal disturbances—diabetes insipidus, precocious puberty, obesity.



Fig. 28.19: Acquired hydrocephalus in a survivor from tuberculous meningitis.

- At times, abnormal movements, paralysis, decorticate or decerebrate spasm or rigidity and other manifestations of raised intracranial tension may be encountered.

Pathology

Histopathologically, the most important and consistent finding is the edema of the brain cells. This change is predominant in white matter though gray matter may also be affected. There may be perivascular or mononuclear reaction. Rarely, frank hemorrhagic spots may be noticed. There is, however, no significant involvement of the meninges though a few tiny tubercles in meninges or brain have been observed in some of the autopsied cases.

Diagnosis

Diagnosis of tuberculous encephalopathy should be seriously considered in a clinical scenario keeping with CNS tuberculosis minus meningeal signs and nearly normal CSF (sometime slight rise in proteins and cells). The presence of miliary, disseminated or intrathoracic tuberculosis helps in recognizing this entity. Even in the absence of clinical evidence of tuberculosis, the diagnosis may be suggested by exclusion of other conditions and, at times, only by brain biopsy on autopsy.

Treatment

It is more or less on the same lines as for TBM.

TUBERCULOMA

Tuberculoma is yet another type of CNS tuberculosis. About one-half of the intracranial space-occupying lesions are accounted by tuberculoma in tropical infants and children.

Etiopathogenesis

Tuberculoma is always secondary to a primary tuberculous lesion elsewhere in the body. Since the host's resistance

is good enough, the bacilli which spread to brain fail to cause meningitis. But they keep forming granulomatous tissue which is infratentorial in majority of the cases. Granulomata may, however, be supratentorial as well as scattered over multiple sites.

Clinical Features

- Unlike other forms of tuberculosis, children suffering from tuberculoma may appear adequately built and well-nourished.
- Manifestations are those of other space-occupying lesions.
- Onset is usually gradual with vomiting, headache, cerebellar ataxia and diminished vision.
- Most of the patients have fever as well.

Diagnosis

Tuberculoma needs to be differentiated from brain abscess, subdural hematoma, brain tumor, neurocysticercosis (NCC), etc.

Diagnostic investigations are on standard lines (already discussed). Neuroimaging (CT or MRI) constitutes the most important modality for diagnosis. It usually is seen as a discrete lesion with a significant amount of surrounding edema (Fig. 28.20), in the form of a ring like lesion which must be distinguished from that of neurocysticercosis (described later in this chapter).

Treatment

Antituberculous chemotherapy should be started as soon as the diagnosis has been made. Some cases may need surgical intervention to reduce the high ICP. Poor response is an indication for surgical excision rather than mere burr holes.

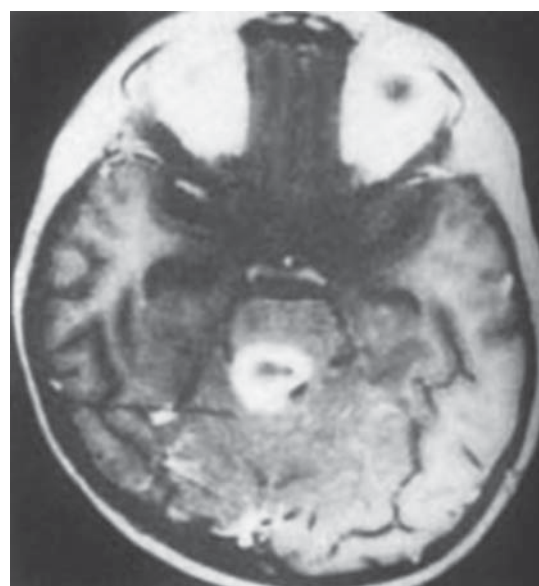


Fig. 28.20: Magnetic resonance imaging demonstrating a tuberculoma. Note the ring like discrete lesion with considerable surrounding edema. Most often, pediatric tuberculoma is solitary and infratentorial, located at the base of the brain near the cerebellum.

528 ENCEPHALITIS (MENINGOENCEPHALITIS)

Definition

The Greek term, *encephalitis*, denotes inflammation of the brain usually due to direct viral invasion via hematogenous route, across olfactory mucosa, or along peripheral nerves, or some immunologic reaction in the nervous system of the host.

Encephalitis vis-à-vis Encephalopathy

When cerebral dysfunction follows a functional metabolic defect in the brain cells or a circulating toxic agent, the condition is called *encephalopathy*.

Encephalopathy may be static, e.g. CP or progressive (e.g. galactosemia, leukodystrophy). There is, however, considerable overlap and the two groups should not be considered as absolutely distinct and airtight compartments.

Etiologic Considerations

The occurrence of viral encephalitis as a complication of measles, chickenpox, mumps, herpes simplex and rabies is well known. In addition, there is a relatively commoner variety of encephalitis which occurs in sporadic as well endemic forms in India and other countries. The vast majority of these cases are of viral etiology though identification of virus has not always been possible. In all probability, enteroviruses are responsible in most. Certain bacterial infections like shigellosis, salmonellosis and scarlet fever may, occasionally, cause toxic encephalitis. Besides, pertussis, enteric fever or tuberculosis may cause an encephalopathy that clinically resembles viral encephalitis.

It is worth mentioning that in some of the outbreaks of encephalitis, encountered during and after monsoon in India, the etiologic agent has proved to be a virus which is similar to Japanese type B serologically. It has been called Tamil Nadu virus. In other epidemic and sporadic cases of viral encephalitis, the etiologic agent appears to be non-Japanese B enterovirus.

In cases of the so-called Nagpur encephalitis or encephalopathy, it appears that, besides, enteroviruses, there may be additional etiologic factors such as other viruses and high environmental temperature. Box 28.21 gives etiologic classification of encephalitis.

Clinical Features

Clinical picture of viral encephalitis is essentially similar, irrespective of the causative viruses. The onset may be acute or gradual. Manifestations include change in sensorium, varying from lethargy to coma, fever, vomiting and convulsions. Some children demonstrate peculiar behavior, hyperactivity, altered speech and ataxia. Headache is common in older children whereas an infant may start off with gross irritability and feeding difficulty.

An inflammatory reaction of meninges may produce some meningeal signs.

Box 28.21**Etiologic classification of encephalitis/ encephalopathy**

- **Viral**
 - **Direct invasion:** Abroviruses (Japanese B, Eastern and Western equine, Russian spring summer), ECHOviruses, Coxsackie viruses, polio, herpes simplex, rabies, mumps measles, rubella, cytomegalovirus
 - **Indirect invasion:** Measles, chickenpox, rubella, varicella, mumps, infectious mononucleosis, influenza, rabies, Guillain-Barré syndrome
- **Bacterial:** Tuberculosis, enteric fever, cerebral abscess (at an early stage), pertussis
- **Spirochetal:** Syphilis, leptospirosis
- **Protozoal:** Toxoplasmosis, malaria, amebiasis
- **Helminthiasis:** Schistosomiasis, cysticercosis, hydatid disease
- **Fungal:** Histoplasmosis, aspergillosis, cryptococcosis
- **Metabolic:** Hyperbilirubinemia of newborn, diabetic ketoacidosis, uremia, hypoglycemia, Reye syndrome, electrolyte imbalance
- **Toxic:** Poisoning by lead, insecticides, carbon monoxide
- **Physical and Environmental:** Hyperpyrexia, heat stroke.

Abbreviation: ECHO viruses, enteric cytopathic human orphan viruses.

Clinical picture shows rapid variation from hour to hour. Confusing neurologic involvements, including tremors and sensory changes, may be observed. Hemiparesis is common; so, are respiratory irregularities. Visual disturbances and facial paralysis occur in some cases. Occasionally, myocarditis and hypotension complicate the picture.

In a number of conditions that could fall under the title progressive encephalopathy, the child exhibits some degree of mental retardation (Box 28.22).

Diagnosis

Diagnosis is essentially clinical and is by exclusion of diseases, such as meningitis, encephalopathy, cerebral malaria, heat stroke and septicemia.

Lumbar puncture should always be done, not because encephalitis has any typical CSF picture but to rule out meningitis. CSF pressure is high but biochemistry is essentially normal. Sugar is either normal or little raised. Same is true of proteins. Slight pleocytosis with predominance of polys in first 48 hours and lymphos afterward may be noticed.

Treatment

- **Specific:** As yet, there is nothing specific that can cure viral encephalitis.

Box 28.22**Progressive encephalopathies causing mental retardation**

- Phenylketonuria (PKU)
- Galactosemia
- Hurler syndrome
- Tay-Sach disease
- Leukodystrophy
- Lesch-Nahan syndrome
- Tuberous sclerosis
- Muscle dystrophy
- Subacute sclerosis panencephalitis (SSPE)
- Kuril encephalitis.

- **Symptomatic:** General supportive measures form the cornerstone of management. It is advisable that such a patient is treated in a hospital. Besides general nursing care, involving attention to skin, bowel, bladder, etc. the following should be done:
 - **Intravenous fluids:** An IV drip is essential to maintain nutrition and fluid and electrolyte balance in initial stages. Later, Ryle tube feeding may be done in cases whose coma lingers over a prolonged period. Vitamin and mineral supplements may be given, if needed.
 - **Antibiotics:** Since, under most situations, it may be nearly impossible to rule out a bacterial infection and since incidence of superadded bacterial infections is high, a good antibiotic shield is recommended. This is especially so in the initial stages of treatment.
 - **Anticonvulsants:** Convulsions should be controlled with phenobarbital, paraldehyde, chloral hydrate, diazepam, lorazepam or diphenylhydantoin sodium. Most cases need anticonvulsant therapy round the clock.
 - **Reduction of hyperpyrexia:** High fever should be controlled by tepid sponging and/or antipyretics.
 - **Reduction of intracranial pressure:** This is achieved by careful repeated withdrawal of CSF or with hypertonic solutions like mannitol given intravenously.
 - **Maintenance of airway:** Frequent suctioning is usually sufficient. Some cases may require tracheostomy and even assisted respiration by a “respirator”.
 - **Corticosteroids:** Most authorities feel that the benefit of steroid therapy should be given. The true value of such a therapy is not established.
 - **Human immunoglobulin:** There is some evidence that IVIG, when given early enough and in high-dose (200–500 mg/kg), may considerably reduce the mortality rate.

Prognosis

It is always guarded. Recently, low serum and CSF magnesium level in acute encephalitis have been found to be associated with prolonged illness and poor prognosis.* The mortality rate is high. Those who survive may be left with sequelae like mental retardation, epilepsy, behavioral disorders, obesity and paralysis.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Definition

Acute disseminated encephalomyelitis (ADEM) is defined as an acute immune demyelination of the brain and spinal cord from varied insults to oligodendroglia.

* This observation holds good for meningitis, both tuberculous and pyogenic.

Etiopathogenesis

Infections and vaccines are responsible for this rare disease. Pathological changes are periventricular in location, usually at the gray-white zone.

Clinical Features

Manifestations in acute stage include seizures, sensorial alterations, visual disturbances, increased ICP and multifocal neurological signs.

Diagnosis

- **Lumbar puncture:** Cerebrospinal fluid (CSF) shows slight pleocytosis and marginal elevation in protein. CSF glucose is normal.
- **Computed tomography scan:** Multiple hypodensities (which enhance with contrast) in white matter.
- **Magnetic resonance imaging:** White matter lesions; spinal cord and basal ganglia lesions.

Treatment

- Treatment, aimed at suppressing the inflammation in the brain, with high doses of steroids. Three to five days course of methylprednisolone given by drip followed by a **tapering schedule** of oral steroid is the usual recommendation.
- If steroids do not work, plasma exchange or IV immunoglobulin therapy are good alternatives. Additionally, physiotherapy and occupational therapy help improve strength, balance and function.

REYE SYNDROME

This is a generalized mitochondrial disorder in which encephalopathy occurs secondary to liver dysfunction, usually following administration of salicylates in a child suffering from an exanthemata such as varicella. Though observed in India way back in 1956 as Jamshedpur fever, it was first described by Reye and coworkers from Australia in 1964.

Reye syndrome may be confused with several disorders (the so-called “Reye-like” diseases) such as CNS infections (meningitis, encephalitis), CNS intoxications (toxic encephalopathy), metabolic diseases (systemic carnitine deficiency), hemorrhagic shock with encephalopathy, drug toxicity (salicylates, valproate) and toxins (hypoglycin A, valproate). For details, See Chapter 30 (Pediatric Hepatology and Pancreatology).

HYDROCEPHALUS

Definition

The Greek term, “hydrocephalus”, literally meaning water logging of the head, refers to the enlargement of the head as a result of abnormally high accumulation of CSF in the intracranial spaces.

530 Whereas incidence of congenital hydrocephalus is not precisely known, acquired hydrocephalus occurs 1 in 1,000 children.

Circulation of Cerebrospinal Fluid

Before embarking on details about hydrocephalus, let us recall the circulation of CSF.

It is the choroid plexus (predominantly that of lateral ventricles) that secretes the CSF. From there, the CSF passes through the foramina of Monro to the third ventricle and then via aqueduct of Sylvius to fourth ventricle. Through foramina of Luschka and Magendie in the roof of the fourth ventricle, it enters into the subarachnoid spaces. Only 20% of it enters the spinal subarachnoid space. The overwhelming amount goes to the subarachnoid villi near the sagittal sinus where it gets absorbed.

Etiology

It may be because of:

- Increased production (communicating hydrocephalus), e.g. pseudotumor cerebri, choroid plexus papilloma
- Obstruction to the flow (noncommunicating hydrocephalus), e.g. inflammatory adhesions, developmental obstructive lesions.
- Interference with absorption, e.g. cavernous sinus thrombosis.

Majority of the patients suffer from the second type, i.e. obstruction in route of CSF flow. Increased production is less frequent. Interference with absorption of the fluid is uncommon and also of poorly understood mechanism. Clinically, the causes are:

- **Congenital hydrocephalus:** It may be associated with:
 - Arnold-Chiari malformation in which there is a displacement of the brainstem and cerebellum, through foramen magnum, into upper cervical part of the spine. It is generally associated with spina bifida and meningocele.
 - Dandy-Walker anomaly in which congenital septa or membranes block the outlet of the fourth ventricle.
 - Malformations or stenotic lesions of aqueduct cerebri.
 - Malformations of arachnoid villi.
- **Acquired hydrocephalus:**
 - Inflammatory meningitis, occasionally encephalitis in first few months of life.
 - Traumatic birth trauma, head injury, intracranial hemorrhage.
 - Neoplastic space-occupying lesions like tuberculoma, subdural hematoma or abscess, gliomas, etc.
 - Chemical hypervitaminosis A.
 - Connective tissue disorders Hurler syndrome, achondroplasia.

Clinical Features

Congenital hydrocephalus is present right at birth or becomes apparent in the first few month of life.

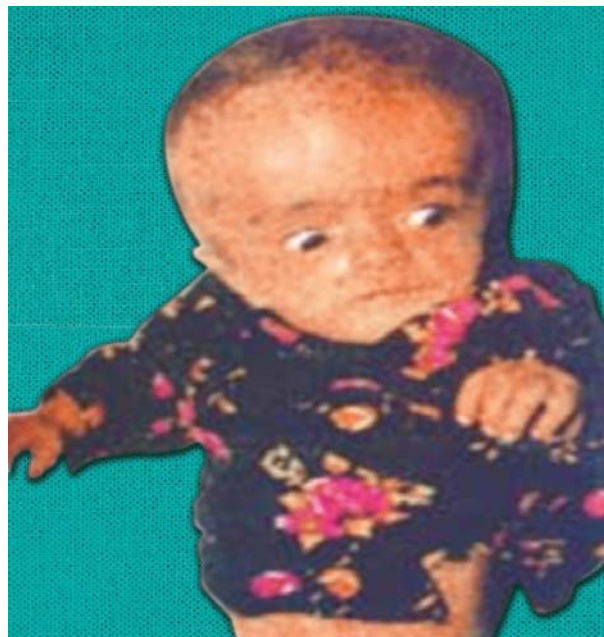


Fig. 28.21: Congenital hydrocephalus. Note the "sunset" sign in the eyes in addition to enlarged head (43 cm) in this neonate.

Acquired hydrocephalus develops later, in association with or as a sequel to the causative factor. Clinical picture is classical with a large head, wide and bulging fontanels, open sutures, protruding forehead and dilated, prominent scalp veins. Scalp appears thin and shiny. The sunset sign, i.e. visible sclera above the cornea, is characteristic (Fig. 28.21). The cracked-pot (Macewen) sign may be elicited by percussing the head. A resonant note as a result of separation of sutures is present. Transillumination is positive.

With steady rise in ICP, the cry becomes shrill. Mental faculty and other neurologic manifestations vary with the causative and associated factor(s). Many are known to have fairly normal intelligence. Arrested hydrocephalus is the term applied when there is no more progression in the head size. This type requires no surgical intervention.

Hydrocephalus occurring late in childhood is not accompanied by big head. Instead there occur manifestations of RIP such as papilledema, spasticity, ataxia, urinary incontinence, and progressive deterioration in mental faculty.

Diagnosis

It is easy to diagnose hydrocephalus. But the aim should be to find out the exact lesion. This may need extensive radiologic studies of the skull, including ventriculography and pneumoencephalography.

CT scan (or MRI) along with ultrasound is the most reliable and safe tool in identifying the site of obstruction in the CSF flow. Differential diagnosis is primarily from megalencephaly or hydraencephaly, chronic subdural effusion or hematoma, cerebral atrophy, and thickened cranium due to rickets, chronic anemia, osteogenesis imperfecta and epiphyseal dysplasia.

Treatment

Medical treatment, aimed at reducing the RIP with hypertonic solutions (mannitol), acetazolamide, frusemide or other diuretics, is, at best, of temporary value. Firm wrapping of the head and third ventriculostomy and choroid plexectomy have been employed with variable results.

Surgical shunts, using tubes which bypass the obstruction and drain the excess CSF to the exterior (ureter, blood, pleural, peritoneal or some other cavity, or into the right atrium), are the treatment of choice at the present time. Indications of bypass shunt are:

- Rapid increase in occipitalfrontal circumference (OFC)
- Threat to vision
- Threat to life.

Quite a few shunts are available. A popular Indian-made shunt is Bhargava shunt. Prognosis after shunt is, however, not uniformly good (Box 28.23).

Revision of shunt indicated in the following situations:

- Complications
- As the child grows.

Intrauterine surgical intervention in fetal hydrocephalus that is frequently accompanied by cerebral malformations has not yet given good results.

Prognosis

Following appropriate medical and neurosurgical treatment, about 70% of patients with infantile hydrocephalus live beyond first year of life. Around 60% of these are likely to have:

- Motor and intellectual handicap in the form of low IQ
- Poor memory
- Visual problems (squint, field defects, optic atrophy)
- Aggressive and delinquent behavior.

A long-term follow-up in a multidisciplinary setting is warranted. Without treatment, mortality is as high as 50–60%.

INTRACRANIAL SPACE-OCCUPYING LESIONS (ICSOL)

Intracranial abnormal lesions, causing RIP and pressure symptoms, are:

- **Inflammatory:** Tuberculoma, brain abscess, subdural effusion
- **Traumatic:** Subdural hematoma
- **Parasitic:** Cysticercosis, hydatid disease

Box 28.23

Complications of bypass shunt in hydrocephalus

- **Short-term**
 - Sepsis of the shunt, usually with *Staphylococcus epidermidis*
 - Obstruction of shunt
 - Bacterial colonization.
- **Long-term**
 - Pulmonary hypertension
 - Cor pulmonale.

- **Tumors:** Astrocytoma, medulloblastoma, glioma, 531 ependymoma, choroid plexus papilloma, cranio-pharyngioma.

BRAIN ABSCESS

Etiopathogenesis

It may result from:

- As a complication of otitis media, mastoiditis, sinusitis or infection of the skull bones
- Hematogenous spread of suppurative conditions such as lung abscess, empyema or bronchiectasis
- Generalized pyemia as in bacterial endocarditis
- Cyanotic congenital heart disease in which the septic emboli find it easy to pass through the right to left shunt and then find a good medium for the growth of the organism in the hypoxic brain tissue. The causative organisms include anaerobic bacteria, *Streptococcus aureus*, *Pneumococcus*, *Hemophilus influenzae*, *Proteus*, *Klebsiella*, etc. Infrequently, fungus and amebic infections may also be responsible for the disease.

The most common location of the abscess is the cerebellum. When it is in the cerebrum, the site is usually in the temporal or frontal lobe. It usually begins as focal suppurative encephalitis. Subsequently, a protective wall develops around the suppuration. Pathologically, the abscess is a layer of vascularized granulation tissue encapsulating pus and other glial cell proliferation.

Clinical Features

- The increased ICP may cause headache, vomiting and visual disturbances
- Depending on the location of the abscess, there may be focal neurologic manifestations such as convulsions, cranial nerve palsies, ataxia, visual field defects, hemiparesis, etc.
- Manifestations of toxemia may include high or low irregular fever, chills, rigors and leukocytosis
- As a result of intracranial suppuration, the child may have irritability, behavioral problems, drowsiness, and loss of weight.

Diagnosis

- Clinical suspicion from the presenting features in a susceptible case
- Demonstration of evidence of pyemia and leukocytosis. ESR may be slightly high
- LP is best avoided, especially in the presence of papilledema because of the danger of herniation and coning of the brainstem
- EEG may be of help in localizing the abscess
- CT scan, MRI or arteriography confirm the diagnosis (Figs 28.22 and 28.23).

Treatment

General measures include management of raised ICP. Aggressive antibiotic therapy should be initiated using IV cefotaxime or ceftriaxone, vancomycin and metronidazole.

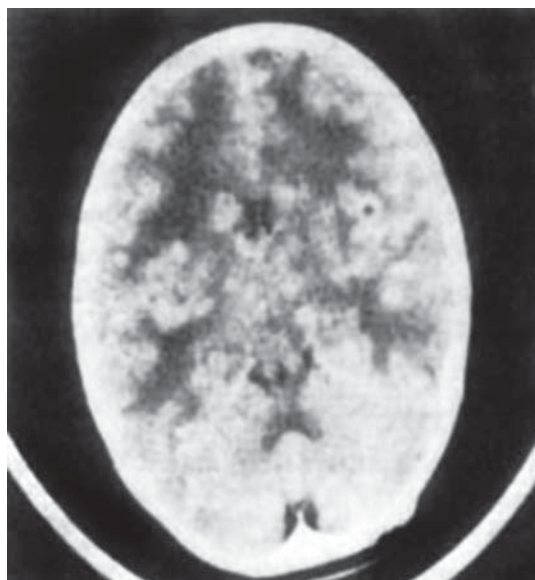


Fig. 28.22: Computed tomography scan showing cerebral abscess in left frontal lobe.

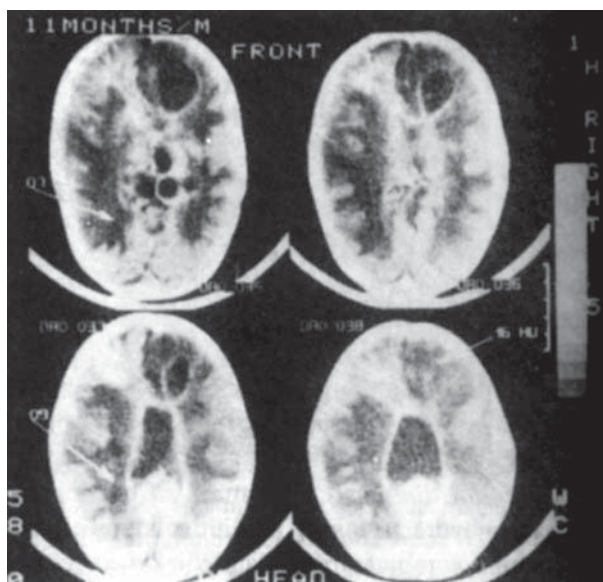


Fig. 28.23: Computed tomography scan showing multiple brain abscesses.

At least a 3-week course is mandatory. Surgical drainage or excision of the abscess is indicated in the following situations:

- Abscess size greater than 2.5 cm
- Abscess location posterior fossa
- Abscess showing gas within it
- Abscess of fungal etiology.

SUBDURAL EFFUSION

Subdural effusion usually occurs in infants as a complication of pyogenic meningitis (in most cases due to *H. influenzae* or *Pneumococcus*). The usual site is frontal or parietal region. The effusion is generally small. Such small effusions may be multiple and, as a rule, clear spontaneously. Large effusions are likely to cause RIP and interfere with recovery from meningitis.

- Clinical features include persistent fever, vomiting, convulsions, irritability or drowsiness, tense and bulging anterior fontanel and progressively increasing hydrocephalus in a case of pyogenic meningitis on adequate therapy

- CSF usually continues to be abnormal
- X-ray skull may reveal sutural diastasis. Increased transillumination of the head may be observed.

Once the existence of subdural effusion is suspected, a subdural tap should immediately be done See Chapter 48 (Miscellaneous and Unclassified Issues).

- Treatment consists in tapping a large effusion daily or on alternate days. Its persistence beyond 2 weeks, despite such taps, is an indication for surgical drainage after craniotomy.

Subdural Hematoma

- Acute subdural hematoma, a common condition in infancy with a peak incidence at 6 months, is invariably due to trauma during birth or later.

- Predisposing conditions include congenital malformations of blood vessels, malnutrition, dehydration and bleeding diathesis. The condition is usually bilateral. The common site is frontal or parietal region.

- Clinical features include progressive deterioration in consciousness, focal convulsions and neurologic signs. Sluggishly-reacting, dilated and unequal pupils, ptosis, squint, facial paralysis, contralateral hemiplegia, meningeal signs, bulging and tense anterior fontanel, hydrocephalus with sutural diastasis and decerebrate rigidity may occur.

- Investigations may show papilledema and retinal hemorrhages, unilateral bulging of skull and sutural diastasis on radiology and frank blood in the subdural tap, which is the most useful tool. Arteriography and radioisotope brain scan may be of helpful. CT scan may be needed to confirm the diagnosis.

- Treatment is repeated drainage of the blood by subdural tap over a period of 2 weeks, or by irrigation through burr holes, and surgical excision of the hematoma.

Subacute subdural hematoma, unlike the acute one, does not manifest immediately after the injury. It takes a few days to do that.

- Chronic subdural hematoma usually follows birth injury or postnatal head trauma. It is particularly more common in preterm babies.

- Manifestations, produced usually about 2 weeks after the trauma, include failure to thrive, irritability, vomiting, fever, drowsiness, convulsions, wasting, bulging fontanel and enlargement (biparietal) of head. Focal neurologic signs are usually not encountered, except in older children in whom papilloedema and hemiparesis may be present.

- Diagnosis is confirmed by subdural tap and radiology, including pneumoencephalography. EEG and angiography may be helpful in difficult situations.
- Treatment consists in draining the hematoma by repeated subdural taps and removing the blood by surgical evacuation, if the response to the former is poor.

NEUROCYSTICERCOSIS

Neurocysticercosis is the most common cause of parasitic CNS disease.

Etiopathogenesis

Cysticercus, sort of granuloma representing intermediate (granulomatous) stage of the pork tapeworm, *Tenia solium*, is a fluid filled sac of variable size. Scolex is a structure which resembles adult *T. solium* and found in invaginated form inside the cysticercus sac. The cysticerci may lodge in brain parenchyma, spinal cord, eyes, ventricular system, subarachnoid space and muscle.

Brain parenchymal cysticerci are usually small cysts, single or multiple, varying from 0.2–0.5 cm in diameter that tends to lodge in areas of high vascular supply.

Clinical Features

Clinical manifestations depend upon number and topography of lesions, the individual immune response to the parasite, and the sequelae of previous infestations.

Common manifestations are partial seizures with secondary generalization or other types of seizures, pyramidal tract signs, sensory deficit, involuntary movements, cerebellar ataxia and unsteady gait, signs of brainstem dysfunction, intellectual deterioration, dementia and psychosis and cysticercotic encephalitis/meningitis. Children with cysticercus encephalitis present with signs of mental disturbances, diminution of visual acuity and generalized seizure. Clinically, differential diagnosis is from CNS tuberculosis (tuberculoma), encephalitis, stroke, etc.

Diagnostic Investigations

Specific diagnostic investigations include neuroimaging studies, the most important being CT scan and/or MRI. A single enhancing ring or disk-like lesion, usually in the parietal region, that is hypodense with irregular margins and an eccentric dot (scolex) is a pathognomonic sign of NCC (Fig. 28.24).

The MRI scores over CT scan in detecting scolex, in delineating evidence of inflammation around the cyst, for intraventricular cysts and for spinal cord cysts. Diffuse or disseminated cysticercosis may show up as the **starry-night** appearance (Fig. 28.25). Both CT and MRI are mutually complementary in providing optimal noninvasive diagnosis. Enzyme-linked immunotransfer blot (ELTB) is a highly specific and sensitive serologic test for cysticercosis.

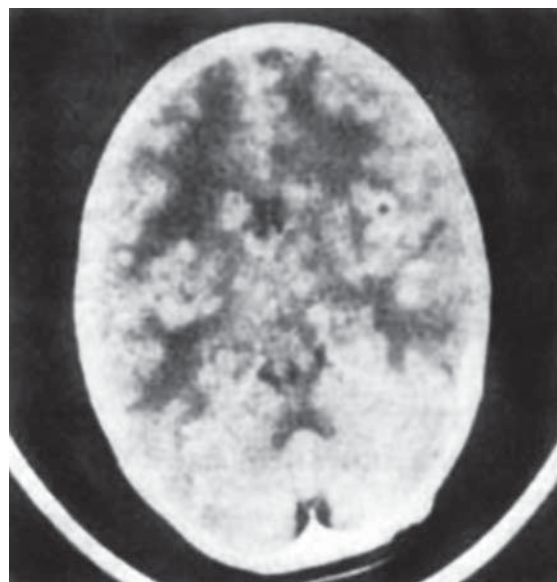


Fig. 28.24: Computed tomography scan (contrast enhanced) showing a single ring-shaped lesion right parietal lobe.

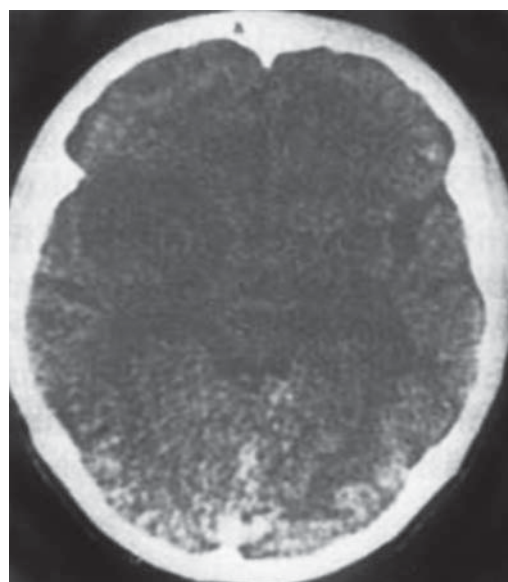


Fig. 28.25: Computed tomography scan showing disseminated (diffuse) neurocysticercosis. Note the **starry-night** appearance.

Treatment

Parenchymal granulomas or calcifications do not require treatment with cysticidal drugs because these lesions represent only the sequelae of previous cysts which were destroyed by the host's immune system.

Medical Therapy

- **Specific cysticidal therapy:** It is indicated only for active and/or disseminated NCC and is in the form of albendazole, 15 mg/kg/day for 5–7 days (there is no added advantage in giving a longer course of 28 days) or praziquantel (PZQ), 50–100 mg/kg/day for 15 days.
- **Antiedema/anti-inflammatory therapy:** To safeguard against worsening of symptoms due to enhanced inflammatory response following specific therapy, it is

- 534 advisable to give steroid therapy (prednisolone 1 mg/kg OD) during the course of treatment, starting 2–3 days prior to actual institution of specific therapy.
- **Antiepileptic therapy:** Phenytoin sodium or carbamazepine for 2–3 months.

Surgical Therapy

It is indicated for intraventricular and subarachnoid NCC. Surgical intervention is indicated in ocular cysticercosis and in placing a ventricular shunt prior to specific therapy of ventricular or spinal disease or parenchymal lesions with hydrocephalus.

Prevention

The main measures for prevention of cysticercosis are proper disposal of human waste, treatment of water contaminated with human feces before its use in irrigation of vegetable cultivation, proper cooking of pork and public education on life cycle of *Tenia solium*.

INTRACRANIAL TUMORS

Tumors are the most common cause of abnormal increase in head size after 2 years of age. A great majority of them are gliomas which are nearly always found in the posterior fossa. The most frequently occurring tumor, astrocytoma, is slow-growing and relatively mild. The next in frequency, i.e. medulloblastoma, is highly malignant. For details, See Chapter 33 (Pediatric Oncology).

CAVERNOUS SINUS THROMBOSIS

This uncommon condition occurs as a complication of a septic focus over face, orbit, nose, teeth, etc. The infection spreads from facial veins to ophthalmic vein and finally to the cavernous sinus. Intracranial extension may be accompanied by meningitis.

Clinical Features

These include high spiking fever, rigors, drowsiness, swelling of affected eye with proptosis, chemosis, and prominent veins over lids and ophthalmoplegia involving 3rd, 4th, 5th and 6th cranial nerves (Fig. 28.26). Pupillary reflexes may be absent and there may be visual defects with, at times, total blindness. Fundoscopy reveals blurred disc margins and engorged retinal veins.

Diagnosis

It is more or less clinical. Orbital cellulitis with localized manifestations is an important differential diagnosis. LP is indicated in a case of doubtful meningitis. Slight rise in CSF proteins may be seen in cavernous sinus thrombosis without meningitis.

Treatment

- High-dose parenteral antibiotic therapy, providing a good cover for *S. aureus*, and anti-inflammatory therapy is given.



Fig. 28.26: Cavernous sinus thrombosis. The child presented with hyperpyrexia, swollen eyes with proptosis, and ophthalmoplegia.

- Drainage of pus from primary septic focus needs to be given a priority.
- Supportive measures, including mannitol for raised intracranial tension, are indicated.
- Anticoagulant therapy is no longer recommended.

CONVULSIVE DISORDERS (SEIZURE DISORDERS)

OVERVIEW AND GENERAL CONSIDERATIONS

Definition

A convulsion or seizure is a transient disturbance of brain function, manifested by involuntary motor, sensory, autonomic, sensorial or psychic phenomenon—alone or in a combination—as a result of abnormal electrical discharges. Associated alteration or loss of consciousness is usual.

Barring neonatal period, tonic and clonic components are the most frequently encountered convulsions. Convulsions need to be differentiated from certain movement disorders (say tremors, dystonias) and other disorders that may mimic them.

Epidemiology

Convulsions are relatively more common in infancy and childhood, the incidence in preschoolers being around 5–6%. The overall incidence in childhood is stated to be 8%. Incidence among mentally retarded children (except those with Down syndrome) is 20%, and among those suffering from CP 35%.

In a recent retrospective study, we found an overall incidence of 15% among inpatients and 11% among outpatients in pediatric departments of tertiary-care hospitals.

Etiology

Convulsions may be categorized in terms of causes according to the age of onset as shown in Box 28.24.

Box 28.24**Causes of convulsions according to the age of onset****0 to 1 Month**

- **First and second day:** Perinatal problems such as birth injury, asphyxia, hypoxia, intracranial (especially intraventricular) hemorrhage—drug (narcotic) withdrawal; pyridoxine dependency; accidental injection of anesthesia into an infant's scalp during labor; inborn errors such as phenylketonuria (PKU)
- **Third day:** Hypoglycemia.
- **Fourth day and onward:** Infections like meningitis, septicemia, hypocalcemia (tetany), hypo- or hypernatremia, hypomagnesemia, kernicterus, tetanus, congenital malformations like arteriovenous fistula, porencephaly, intrauterine infections like syphilis, toxoplasmosis, rubella, cytomegalic inclusion disease, herpes simplex (STORCH).

1 to 6 Months

- **CNS Infections:** Meningitis, encephalitis, enteric fever, cerebral malaria, intrauterine infections.
- **Metabolic:** Hypoglycemia, hypocalcemia, hypernatremia, hypomagnesemia, inborn errors of metabolism like glycogen-storage disease, kinky hair syndrome.
- **Traumatic:** Nonaccidental injury, chronic subdurals.
- **Congenital malformations:** Arteriovenous fistulae.
- **Space-occupying:** Brain tumor, abscess, tuberculoma, cysticercosis.
- **Vascular:** Intracranial hemorrhage, DIC, hypertension.
- **Drugs:** Phenothiazines, strychnine, piperazine, lead.
- **Postvaccinal:** DPT.

6 Months to 3 Years: Febrile convulsions plus previously enumerated conditions at B.

3 to 6 Years: Idiopathic epilepsy; febrile convulsions uncommon; rest as previously enumerated at B.

Abbreviations: DIC, disseminated intravascular coagulation; DPT, Diphtheria, pertussis, tetanus.

Diagnosis

It is based on good history and physical examination plus certain investigations depending on merits of the case.

- History should seek information concerning onset, aura, duration, pattern, postictal loss of consciousness/drowsiness or weakness of a body part
- Physical examination aims at finding out mental status, any dysmorphism, congenital malformations, level of sensorium, paresis/paralysis, etc. Fundoscopy should always be done after the acute attack has been brought under control.
- Investigations include:
 - **Biochemical:** Blood glucose, calcium, phosphorous, especially in neonatal seizures and suspected tetany.
 - LP in select cases after the acute attack is over.
 - EEG is helpful for confirming suspected seizure, characterizing type of seizure, localizing epileptic focus and finding its anatomical basis. In petit mal epilepsy, for instance, 3 per second spikes and wave complexes are diagnostic.
 - **Cranial imaging:** Indications for CT scan and/or MRI are:
 - EEG suggesting focal abnormalities
 - Parietal seizures

- Seizures with focal neurological deficit
- Seizures with dysmorphism
- Seizures with skin lesions
- Seizures with raised ICP.

CT scan/MRI can be helpful in detecting vascular malformations, inflammatory lesions, neoplasms, space-occupying lesions, etc. Pneumoencephalography, arteriography and radioisotope brain scan may be of special value in cases of persistent localizing signs. X-ray skull is good enough for detecting calcified lesions.

Treatment

In addition to the pharmacotherapy (vide infra), supportive care is mandatory for optimal outcome.

FEBRILE SEIZURES**Definition**

The term denotes seizures associated with fever (but excluding those due to CNS infections) occurring in neurologically normal children in the age group 3 months to 5 years.

Incidence

Peak incidence occurs at 6 months to 3 years of age. It is one of the most common disorders of infancy and early childhood, accounting for 50% of all convulsive disorders of pediatric age group. Overall incidence in childhood is about 4%. Boys are affected nearly twice as frequently as girls.

Special Features

- **Simple febrile seizures (typical or benign febrile seizures):**
 - These are generally associated with fever of 38°C or more at the time of attack, usually with rapid rise in temperature
 - The attack occurs within 24 hours of onset of fever without recurrence within 24 hours
 - The attack lasts less than 10–15 minutes
 - Usually a single attack per febrile episode
 - Generalized rather than focal convulsions are nearly a rule
 - Family history of seizures is frequently present in siblings
 - Also, higher incidence occurs in twins and children of consanguineous parents. This has led to the speculation that, as a result of genetic susceptibility, immature neuronal membrane responds to the temperature elevation by breaking down
 - There is no residual neurological deficit, e.g. paralysis of a limb following the attack
 - CSF after the attack is normal
 - EEG after the attack is normal.
- **Complex febrile seizures (atypical febrile seizures):** A proportion of children may have focal convulsions

of greater than 10 minutes duration even without significant fever, and/or with persistently abnormal EEG for two weeks or more after the attack.

All these cases (in fact all cases of febrile seizures not satisfying the criteria laid down for typical febrile seizures) are labeled **atypical** or **complex** febrile convulsion cases. Children having complex febrile seizures are predisposed to idiopathic epilepsy.

Treatment

Treatment consists in controlling the acute attack of seizures, bringing down the fever and treating the cause of high temperature which is usually a respiratory infection.

- An anticonvulsant is indicated in the event of a prolonged attack (exceeding 3 minutes). Phenobarbital, 5.0 mg/kg/dose (IM, IV) or diazepam, 0.3–0.5 mg/kg/dose (IV) or 0.5–1 mg/kg (rectal) with a maximum of 10 mg usually suffices. Rectal diazepam has the advantage that it can be administered by paramedical staff and even by parents at home. It is available in India (Direct 2) as a kit enclosing a colored bottle providing 25 mL of 2 mg/mL diazepam solution, a 5 mL syringe and 10 disposable adopters. Midazolam (nasal or buccal) is also effective in acute seizure control.
- Reduction of body temperature may be achieved by tepid water sponging (hydrotherapy) and/or antipyretics like paracetamol, ibuprofen or mefenamic acid.

Prophylaxis (Long-term Treatment)

Whereas parents must be advised to employ antipyretic measures as and when the body temperature is likely to shoot up in all cases of febrile seizures, long-term anticonvulsant therapy is not needed for “simple” febrile seizures. Anticonvulsant drug prophylaxis is usually needed in complex febrile seizures as follows:

- **Intermittent prophylaxis:** Diazepam, given orally during first 3 days of fever, is the preferred modality. Lorazepam, midazolam, clonazepam, and clobazam are effective alternative agents.
- **Continuous prophylaxis:** Oral phenobarbital (5 mg/kg/day) or sodium valproate (10–20 mg/kg/day), given for 1–2 years or until 5 years of age (whichever is earlier), is recommended in the situations listed in Box 28.25.

In view of adverse effects of phenobarbital on cognition and behavior, sodium valproate should be the preferred choice.

Box 28.25

Indications of continuous prophylaxis in febrile seizures

- Subject who fail to respond to intermittent prophylaxis
- Associated central nervous system disease (say mental retardation)
- Recurrent complex febrile seizures
- Positive family history of epilepsy.

Prognosis

It is very good in simple febrile seizures. In complex variety, outcome is less gratifying with high incidence of intellectual impairment, behavior disturbances and epilepsy.

EPILEPSY

Definition

It is defined as a symptom complex characterized by recurrent, paroxysms of unconsciousness or impaired consciousness, usually with a succession of tonic or clonic muscular spasms or other abnormal behavior. Epilepsy is not the same as epilepsy-simulating states and epilepsy equivalents such as narcolepsy, hysteria, breath-holding spells, syncope and migraine.

Classification

- **Conventional classification:** Conventionally, epilepsy is classified as idiopathic or organic.
- **Idiopathic epilepsy:** The salient feature(s) of types of idiopathic epilepsy are as follows:
 - **Grand mal:** Most common; generalized tonic-clonic convulsions are its hallmark.
 - **Petit mal:** Momentary loss of consciousness.
 - **Jacksonian or focal:** Seizures starting from one part and spreading to other parts in a fixed pattern.
 - **Psychomotor (temporal lobe):** Visceral symptoms like nausea, vomiting or epigastric sensations followed by short periods of increased muscular tonicity and, later, semipurposeful movements during a period of impaired consciousness or amnesia.
 - **Myoclonic:** Involuntary violent contractions of limbs or groups of muscles with or without loss of consciousness. In infantile myoclonic epilepsy, also called **salaam seizures or West syndrome**, the baby (usually under 6 months) has massive attacks of flexion of the head, once or as many as 100 times a day. In the primary type child is microcephalic and mentally retarded. EEG shows typical hypsarrhythmia.
- **Organic epilepsy:** It is frequently accompanies CP, mental retardation and other such disorders (Box 28.26). EEG abnormalities are invariably present.
- **Modern classification:** Box 28.27 presents the current classification of epilepsy as per International League Against Epilepsy (ILAE). The old terminology wherever it is at variance and relevant is given in brackets.

Brief Description of Major Types

Tonic-Clonic Seizures

This most common type of epilepsy is characterized by aura, tonic phase, clonic phase and postictal phase. Aura denotes certain vague symptoms (sensory, visceral, motor, autonomic) that warn the patient about the

Box 28.26 Causes of organic epilepsy

- **Post-traumatic:** Direct damage to brain tissue as following head injury.
- **Posthemorrhagic:** Injury to brain at birth or afterward, bleeding diathesis, rupture of miliary aneurysm, pachymeningitis.
- **Postinfectious:** Meningitis, encephalitis, cerebral abscess, sinus thrombophlebitis.
- **Post-toxic:** Kernicterus, chronic poisoning (lead, arsenic).
- **Degenerative:** Intracranial neurofibromatosis, cerebromacular degeneration, subacute sclerosing panencephalitis.
- **Congenital:** Arteriovenous aneurysm, Sturge-Weber type of vascular anomaly, cerebral aplasia, porencephaly, hydrocephalus, tuberous sclerosis.
- **Parasitosis:** Cysticercosis, hydatid disease, ascariasis, toxoplasmosis.

Box 28.27 International League against epilepsy classification of epilepsy**Generalized**

- Tonic-clonic (grandmal)
- Tonic
- Clonic
- Absence (petitmal)
- Atonic/akinetic (minor motor)
- Bilateral epileptic myoclonus syndromes.

Idiopathic

- Benign neonatal
- Childhood absence
- Juvenile absence
- Juvenile myoclonic
- Grandmal on awakening
- Generalized idiopathic.

Cryptogenic

- West syndrome (infantile spasms)
- Lennox-Gastaut syndrome (childhood epileptic encephalopathy)
- Myoclonic-astatic seizures
- Myoclonic absences

Localized (Partial) Seizures

- **Simple partial (without impaired consciousness):**
 - Motor symptoms
 - Sensory symptoms
 - Autonomic symptoms
 - Mixed symptoms
- **Complex partial (with impaired consciousness):**
 - Simple partial, but loss of consciousness
 - With automation

Syndromes

- **Symptomatic**
 - Chronic progressive epilepsy
 - Epilepsia partials continua
- **Idiopathic**
 - Benign childhood focal epilepsy with centrotemporal spikes (Rolandic epilepsy)
 - Epilepsy with occipital paroxysms

Undetermined Syndromes

- Neonatal seizures
- Severe myoclonic epilepsy of infancy
- Epilepsy with continuous spike waves during slow wave sleep
- Acquired epileptic aphasia.

impending attack of seizures. **Tonic phase**, lasting for 30 seconds, is characterized by contraction of skeletal muscles, classically in the flexors of arms and extensors of legs. A shrill cry is produced as a result of contraction of the laryngeal muscles which forces the air out from lungs.

The patient becomes unconscious with frothing from the mouth, pallor of the face, eyes turned upward or sideward and pupils dilated. He may pass urine and stools involuntarily.

Clonic phase, lasting a few minutes, is characterized by alternating rhythmic contractions of muscle groups. **Postictal phase** is characterized by confusion, automatic actions and headache.

Absence Seizures

These seizures, lasting less than 30 seconds, are characterized by momentary loss of consciousness manifesting in the form of brief missing of ongoing activity (say writing) accompanied by a spell of staring, fluttering of eyes or rhythmic movements. Unlike tonic-clonic seizures, there is no aura (hyperventilation may occur for 2–3 minutes preceding attack), loss of posture and involuntary passage of urine and stools, postictal drowsiness, confusion and headache. Multiple attacks in succession (pyknolepsy or petit mal status) may occur. ECG shows a typical 3 per second spike and slow. In 50% cases, absence seizures may pass on to develop tonic-clonic seizures.

Partial Seizures

These are characterized by motor, sensory, autonomic or mixed manifestations secondary to focal lesions in the brain. **Simple partial seizures** are without loss of consciousness and are secondary to a focal epileptiform discharge. Manifestations are motor or sensory (tingling, pain, burning, etc.). The term **Jacksonian march** denotes spreading of such seizures from one area to the other depending on the representation in the motor area of the brain (precentral gyrus).

Complex partial seizures with motor manifestations are characterized by impairment of consciousness, automatism and psychomotor or limbic system manifestations. It originating from temporal lobe, also called **psychomotor epilepsy** and **temporal lobe epilepsy**, are characterized by a visual or olfactory aura followed by unilateral dystonia, tonic jerks of face and/or limbs, peculiar posture, lip smacking, chewing, finger-tightness, complex automation acts, etc.

Visceral symptoms like nausea, vomiting or epigastric sensations followed by short periods of increased muscular tonicity and, later, semipurposeful movements during a period of impaired consciousness or amnesia. The syndrome of periodic headache in association with abdominal pain, nausea and vomiting has been termed **abdominal epilepsy** or **abdominal migraine**.

Syndrome of Benign Childhood Epilepsy with Centrotemporal Spikes

Presumed to be autosomal dominant, it accounts for 25% epilepsy cases in mid childhood (Box 28.28).

Box 28.28**Characteristics of syndrome of benign childhood epilepsy with centrotemporal spikes**

- Simple partial seizures with motor signs usually occur during sleep. Tingling, numbness and other abnormal sensations of lips and tongue, dysarthria and somatosensoryusual manifestations
- Self-limiting with spontaneous remission as the child approaches adolescence
- Onset at 2–13 years
- IQ normal
- Neurological deficit nil
- Interictal electrocardiogram—a spike focus over centrotemporal (Rolandic) area.

Myoclonic Epilepsies

Myoclonic seizures are characterized by involuntary violent contractions of limbs or groups of muscles with or without loss of consciousness.

Infantile Myoclonic Epilepsy

Also called *infantile spasms*, *salaam seizures* or *West syndrome*, the baby (usually 3–8 months) has massive attacks of flexion of the head, once or as many as 100 times a day.

Two types are known. In the primary type child is microcephalic and mentally retarded. Secondary type is the outcome of:

- Hypoxic-ischemic encephalopathy (HIE)
- Tuberous sclerosis and other neurocutaneous syndrome, tonic-clonic, atypical absence
- Perinatal infections
- Metabolic disorders
- Localized malformations in brain
- Intracranial bleed.

EEG shows typical hypsarrhythmia. Treatment is preferably with adrenocorticotrophic hormone (ACTH) though steroids, vigabatrin, diazepam, sodium valproate and pyridoxine may also prove effective to some extent. Prognosis is not good.

Lannox-Gastout Syndrome

A diffuse encephalopathy, it is characterized by myoclonic seizures in association with generalized tonic-clonic, atypical absence or partial seizures. Etiologic conditions include:

- Hypoxia
- Head injury
- CNS infections
- Postvaccination
- Cardiopulmonary arrest.

EEG shows 2 per second spike wave discharges. Pharmacotherapy revolves around ACTH, sodium valproate, lamotrigine, zonisamide, topiramate, benzodiazepines. Prognosis is not good.

Neonatal Seizures

In about 25% neonates with seizures, the cause is metabolic, e.g. hypoglycemia, hypocalcemia, hypomagnes-

semia, etc. In others, the cause may be a serious infection (meningitis, sepsis), hypoxia/asphyxia, etc. As a result of poor myelination and dendritic arborization, neonatal seizures present as:

- Subtle seizures
- Focal clonic seizures
- Focal clonic seizures
- Multifocal clonic seizures
- Myoclonic seizures.

For details, See Chapter 17 (Neonatology).

STATUS EPILEPTICUS

Status epilepticus, a life-threatening emergency, is conventionally defined as a seizure lasting for more than 30 minutes or recurrent seizures for more than 30 minutes during which the patient does not regain consciousness.

According to a modified definition of status epilepticus, considered to be more practical and operational in case of children greater than 5 years of age, duration greater than 5 minutes of continuous seizures or two or more discrete seizures between which incomplete recovery of consciousness should be considered status epilepticus. This definition emphasizes need for early institution of treatment, i.e. within 5–10 minutes in order to safeguard against serious complications, especially neuronal injury.

Refractory status epilepticus is the seizure episode that persists in spite of administration of two appropriate anticonvulsants at acceptable doses. The minimum duration of 60 minutes is no longer considered an essential component of the definition. Predictive situations include:

- Encephalitic etiology
- Severe impairment of consciousness (at time of presentation)
- No previous history of epilepsy
- Low blood levels of anticonvulsant drugs.

Super-refractory status epilepticus is the seizure episode that continues for 24 hours or more after the onset of anesthesia, including those cases the status epilepticus recurs on the reduction or withdrawal of anesthesia. In a large majority of the status epileptics in infants and young children, etiology is *febrile seizures* or *acute symptomatic*. In older children it is *cryptogenic* or *remote symptomatic*.

Metabolic causes of status epilepticus include mitochondrial diseases, lipid storage disorders, aminoacidopathies, organic acidopathies, etc. Pyridoxine dependency, drug or toxin intoxication, autoimmune encephalopathies are also responsible for status epilepticus in a small proportion of cases. An important feature of the treatment of status epilepticus is the prompt institution of vigorous initial therapy rather than small doses of various anticonvulsant drugs.

At times, recovery from status may be followed by weakness of a limb or two for 12–24 hours (or infrequently a week or so). Resolution is slow but, as a rule complete. However, occasionally, minimal weakness may persist.

This is what is called *Todd paresis*. This, the *postictal paralysis*, was believed to be due to metabolic exhaustion of epileptic neurons. Today it is regarded to be a sequel to persistence of active inhibitory state which produces clonic phase of the seizures.

Drug Therapy of an Acute Convulsive Episode

A large number of drugs are available. The best is diazepam, 0.3–0.5 mg/kg, IV, stat*. Half of this dose may be repeated in 10–20 minutes, if necessary or Lorazepam, 0.1 mg/kg, IV (maximum 4 mg) or Midazolam, 0.15–0.2 mg/kg, IV/IM (maximum 5 mg). Since the action of benzodiazepines lasts just 1/2–1 hour, it should be followed by maintenance dose of phenobarbital, 5 mg/kg/day, to protect against recurrences.

For control of acute attack, if diazepam, lorazepam or midazolam is not available, drugs like injectable valproate, phenobarbital, phenytoin/fosphenytoin, paraldehyde, or chloral hydrate may be used. Figure 28.27 presents an algorithmic approach for emergency management of an acute convulsive episode.

DRUG THERAPY OF STATUS EPILEPTICUS

Out of Hospital Treatment

Rectal diazepam, buccal midazolam/lorazepam, intranasal midazolam

Hospital Treatment

■ Immediately on arrival (0 minute)

Injection lorazepam, 0.1 mg IV (maximum 4 mg)

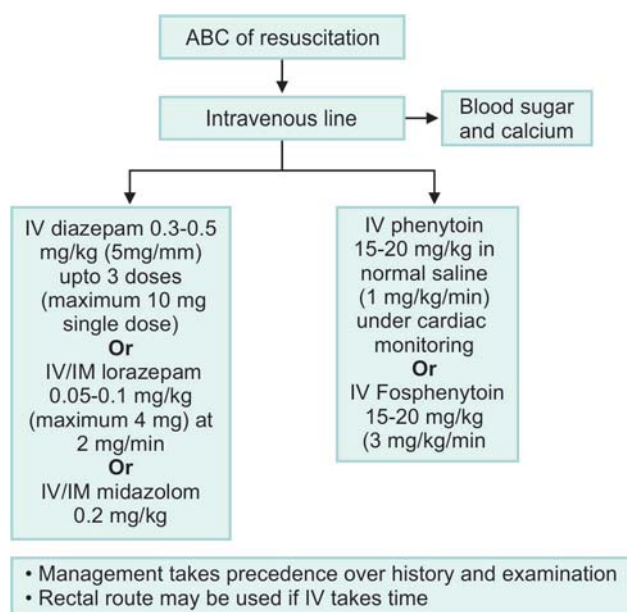


Fig. 28.27: Algorithmic approach for emergency management of an acute convulsive episode.

Abbreviations: ABC, airway, breathing and circulation; IV, intravenous.

* Maximum single dose must not exceed 10 mg.

OR

Injection diazepam, 0.2–0.3 mg/kg IV (maximum 10 mg)

OR

Injection midazolam, 0.15–0.2 mg/kg IV (maximum 5 mg)

- (5 minute) (Unsatisfactory response)
- (10 minutes) (Unsatisfactory response)
 - Repeat dose of one of the benzodiazepines employed earlier
 - Phenytoin/Fosphenytoin, 20 mg/kg IV (maximum 1 g)
- **Refractory seizures (Unsatisfactory response despite above therapy)**
 - If transferred to pediatric intensive care unit (PICU): Midazolam IV infusion.
 - If not transferred to PICU: Valproate 20 mg/kg IV OR Phenobarbital, 20 mg/kg IV OR Levetiracetam, 20–30 mg/kg IV (in subjects with liver disease, metabolic disease, coagulopathy or on chemotherapy).
- **Indications for mechanical ventilation**
 - Glasgow coma scale scores less than 8
 - Respiratory depression
 - Fluid refractory shock
 - Raised ICP
 - Difficulty in maintaining airway patency.
- **Indications for continuous EEG monitoring**
 - Prolonged altered sensorium following cessation of clinical seizures
 - Clinical suspicion of nonconvulsive status epilepticus
 - As and when IV anesthetic agents are administered.

LONG-TERM ANTIEPILEPTIC DRUG THERAPY

Table 28.3 lists the dosage, indications and adverse drug reactions (ADRs) of currently recommended antiepileptic drugs (AEDs).

Tonic-clonic Seizures

Though quite a few AEDs are available, for long-term drug therapy only selected agents are employed. Phenobarbital, phenytoin, sodium valproate and carbamazepine the commonly employed first line AEDs. As a rule, monotherapy should be the choice. To begin with, the lowest effective dose needs to be started. It may be increased in increments if required. If it fails to attain seizure-free state, it should be gradually tapered and an alternative drug introduced. Play therapy may be considered in case of failure of monotherapy in maximum doses.

Generally speaking, duration of therapy varies from 2–4 years. ADRs of long-term administration of phenobarbital include behavioral problems, hyperactivity,

Table 28.3: Salient features of commonly employed antiepileptic drugs

AED	Dose	Indication(s)	ADR
Phenobarbital	3–8 mg/kg/day OD or two divided doses	Febrile seizures Tonic-clonic	Drowsiness in the beginning; behavioral problems, rickets
Phenytoin/ Fosphenytoin	5–10 mg/kg/day OD or two divided doses	Tonic-clonic seizures	Gum hyperplasia, hirsutism, megaloblastic anemia, rash, encephalopathy with seizures, rickets
Sodium valproate	20–60 mg/kg/day in two to three divided doses	Almost all types of seizures	GI upset, drowsiness, hair loss, weight gain, hepatotoxicity
Carbamazepine	10–30 mg/kg/day in a single dose or two divided doses. Low dose is only for takeoff.	Tonic-clonic, partial, atonic, akinetic	GI upset, rash, hepatic insufficiency, bone marrow depression
Clonazepam	0.02–0.2 mg/kg/day in two to three divided doses	Atonic, akinetic, refractory absence seizures	Drowsiness, somnolence, fatigue, hypotonia
Ethosuximide	20–25 mg/kg/day in a single or two divided doses	Absence seizures	GI upset, drowsiness, photophobia, myasthenia syndrome, leucopenia, blood dyscrasia
ACTH	20–40 units OD (IM) × 4–6 weeks Then 10–20 units OD (IM) × 12–24 weeks	West syndrome (infantile spasms)	Cushing disease, euphoria, psychosis, immunosuppression, superadded infections (fungus, Mycobacterium tuberculosis), acne, cataract, skin and muscle atrophy, adrenal suppression
Levetiracetam	10–60 mg/kg/day in two divided doses	Generalized, partial, myoclonus, photosensitive epilepsy	Drowsiness, behavioral problems, especially in children with mental retardation, flu-like syndrome
Lamotrigine	5–10 mg/kg/day With valproate, dose is only 1–5 mg/kg/day With phenobarbital, dose is 10–15 mg/kg/day	Partial, absence; myoclonic, atonic, Lennox-Gastaut syndrome	Drowsiness, blurring of vision
Topiramate	5–10 mg/kg/day in two or three divided doses	Partial (refractory), Generalized (secondary)	Weight loss, neuropsychiatric symptoms, acidosis
Tiagabine	Start with 0.2 mg/kg/day. Increase in increments to 4–6 mg/kg/day. A good “add on”	Partial (both with and without generalization)	Urbation of primary generalized seizures unsteadiness, exac
Vigabatrin	50–150 mg/kg/day in two or three divided doses	Partial (both simple and complex), infantile spasms (tuberous sclerosis)	Drowsiness, easy fatigability, peripheral vision loss, retinal degeneration
Clobazam	0.3–2.0 mg/kg/day as a single dose or in two divided doses	Partial, generalized Partial A good “add on”	Drowsiness, drooling, hyperactivity, ataxia
Tiagabine	0.2–5 mg/kg/day (low dose is for the beginning)	Partial seizures A good “add on”	Unsteadiness, exacerbation of primary generalized seizures
Zonisamide	2–10 mg/kg/day in two divided doses	Partial seizures Progressive myoclonic seizures Refractory infantile seizures infections	Weight loss, renal calculus
Gabapentin	30–60 mg/kg	Partial Secondarily generalized tonic-clonic A good “add on” as well as monotherapy problems	Drowsiness, somnolence, dizziness, headache, ataxia nystagmus, tremors, diplopia
Primidone	<8 years 10–25 mg/kg/day >8 years 125–1,500 mg/day	Partial seizures Secondarily generalized seizures	Intense sedation, dizziness nausea, rhinitis, vomiting behavioral disorders
Oxcarbazepine	10–45 mg/kg/day	Tonic-clonic, partial, atonic, akinetic	Somnolence, ataxia, rash, hyponatremia, alopecia, weight gain
Nitrazepam	0.25–1 mg/kg/day in a single or two divided doses	Partial seizures, infantile Spasm	Paradoxical stimulation, behavioral disorders, irritability, excessive sweating, blurring of vision, dryness of mouth, urinary incontinence
Acetazolamide	8–30 mg/kg/day in three to four divided doses	Refractory epilepsy	Drowsiness, confusion, anorexia, weight loss, rash, hepatic insufficiency, Sensory symptoms (paresthesia)

irritability, quarrelsomeness and sleep disturbances. Since the problems become quite troublesome in some instances, a substitute drug is often given sooner or later. Carbamazepine is of special value in grand mal epilepsy, and temporal lobe seizures to counter the usual problem of psychosomatic deterioration.

Absence Seizures

Ethosuximide is the drug of choice in view of the serious toxicity of trimethadione. Sodium valproate, clonazepam and lamotrigine should be considered alternative choice.

Complex Partial Seizures

Carbamazepine is the drug of choice. In poor responders, a newer AED, polytherapy or surgery may be considered.

Myoclonic Seizures

Adrenocorticotrophic hormone or steroids (prednisolone) is the first choice. Sodium valproate, clonazepam or clobazam should be considered an alternative choice.

Duration of AED Therapy

Long-term anticonvulsant therapy is continued for about 2–4 years of seizure-free period. The drug(s) should never be withdrawn abruptly. Instead, the dosage should be tapered gradually over a period of some months. Usually around 2–3 months suffice for withdrawing the therapy in tapering doses. This can be done without obtaining help from EEG. A longer duration of around one year for gradual withdrawal of therapy has also been suggested. In certain unfavorable situations (juvenile myoclonic epilepsy), AED therapy needs to be continued lifelong.

INTRACTABLE SEIZURES

Definition

The term refers to a group of epilepsies that fail to respond to usually effective anticonvulsant therapy given in maximum tolerated dosage (therapeutic and even supratherapeutic range). The incidence is around 25% of all children with epilepsy. Most important factor contributing to intractability is the poor or noncompliance in some form.

Epilepsies Vulnerable to Intractability

Common epilepsies likely to become intractable include:

- Complex partial seizures
- Myoclonic seizures
- Neonatal myoclonic encephalopathy
- Early infantile epileptic encephalopathy
- West syndrome
- Lennox-Gastaut syndrome
- Epilepsy with myoclonic absences
- Severe myoclonic epilepsy of infancy
- Progressive myoclonus epilepsy.

Diagnostic Evaluation

It should include re-evaluation of history and examination, patient's compliance and drug-drug interaction,

determination of drug levels periodically, MRI, PET or SPECT scanning, and prolonged EEG video monitoring. The last is especially useful when pseudoseizures/other nonepileptiform disorders are on the card.

Treatment

Pharmacotherapy

To begin with, it is with high dose monotherapy. Monotherapy employing five major drugs, namely phenobarbital, phenytoin, carbamazepine, primidone and valproic acid may be tested in maximum therapeutic and even supratherapeutic doses. In case seizures still remain uncontrolled, two first line drugs may be combined or, alternatively, another anticonvulsant like methasuximide, ethosuximide, or acetazolamide added. If the second drug too fails to work, yet another can be tried.

Ketogenic Diet

Ketogenic diet (KD), i.e. a high fat diet, in use since 1921 as a treatment option for many of the children where conventional anticonvulsant agents fail, may be tried in situations such as Lennox-Gastaut syndrome which is known for good response to KD.

- The KD is high in fat, moderate in protein, and low in carbohydrates. The typical KD, called the **long-chain triglyceride diet**, provides 3–4 grams of fat for every 1 gram of carbohydrate and protein.
- The dietician recommends a daily diet that contains 75–100 calories for every kilogram (2.2 pounds) of body weight and 1–2 grams of protein for every kilogram of body weight. If this sounds complicated, it is! That's why parents need a dietician's help.

A KD "ratio" is the ratio of fat to carbohydrate and protein grams combined. A 4:1 ratio is more strict than a 3:1 ratio, and is typically used for most children. A 3:1 ratio is typically used for infants, adolescents, and children who require higher amounts of protein or carbohydrate for some other reason. This combination of energy results in a sustained ketosis that somehow serves to abate seizures through an unknown mechanism. Strict adherence to the diet is required for it to be effective.

Role of Surgery in Epilepsy

Surgical therapy is indicated when medical therapy fails or is accompanied by untoward side-effects. It may be in the form of resection (say lobectomy) or palliative procedure (say corpus callosotomy).

INFANTILE TREMOR SYNDROME

Tremors are a leading manifestation of infantile tremor syndrome (ITS), the other features being significant anemia, regression of developmental and mental milestones, kwashiorkor-like hair changes and skin pigmentation. Tremors are distal in the beginning, but as the condition worsens, these involve the whole body. Their site of origin seems to be **cortical**. For details, See Chapter 42 (Neuromuscular Disorders).

Box 28.29 Stages of coma

- **Stage 0:** Asleep, arousable
- **Stage 1 (Stupor):** Comatose but can be aroused briefly, reflexes intact, responds to verbal and painful stimuli
- **Stage 2 (light coma):** Comatose and cannot be aroused easily, respiration normal, some reflexes absent, responds to painful stimuli
- **Stage 3 (deep coma):** Comatose, respiration normal, most reflexes absent with no response to painful stimuli. Two types of posturing develop (1) intact brainstem—arms flexed on chest, fists closed, legs extended (decorticate posture). (2) involvement of midbrain—all limbs extended (decerebrate posture)
- **Stage 4 (brain death):** Comatose, all reflexes absent (except local spinal reflexes which may remain intact), respiratory failure and/or circulatory failure (shock).

COMA

By definition, coma is an altered state of consciousness with reduced capacity for arousal and reduced responsiveness to various stimuli, visual, auditory and tactile. Accompanying coma may be respiratory failure with cyanosis and/or circulatory failure with shock. It is a medical emergency needing prompt action.

Stages

Box 28.29 lists the various stages of coma.

MODIFIED GLASGOW COMA SCALE

Table 28.4 gives the modified Glasgow coma scale which assists in evaluating progress of cases with unconsciousness of varying stages.

Etiopathogenesis

A number of conditions can cause coma (Box 28.30). Dysfunction of the ascending reticular activating system (ARAS) of the brainstem, hypothalamus or cerebral hemisphere is the main pathological state responsible for coma. Box 28.31 gives a broad mnemonic for causes of coma.

Emergency Measures

While recording the history and physical examination or ordering investigations, it must be ensured that emergency measures have been instituted (Box 28.32).

Diagnosis

History

Interrogate about diabetes, head injury, CNS disease, renal disease, hepatic disease, poisoning, drug overdose and epilepsy.

Physical Examination

Valuable clues are usually obtained from such an examination.

- Pattern of respiration:
 - **Cheyne-strokes:** Involvement at thalamic level (deep cerebral or diencephalic lesion)
 - **Irregular hyperventilation:** Damage to brainstem (midbrain or pons)

Table 28.4: Modified Glasgow coma scale

Eyes opening

Score	Over 1 year	Under 1 year
4	Spontaneous	Spontaneous
3	To verbal command	To shout
2	To pain	To pain
1	No response	No response

Best motor response

Score	Over 1 year	Under 1 year
6	Obeys	Spontaneous
5	Localizes pain	Localizes pain
4	Flexion withdrawal	Flexion withdrawal
3	Flexion abnormal (decorticate rigidity)	Flexion abnormal (decerebrate rigidity)
2	Extension	Extension
1	No response	No response

Best verbal response

Score	Over 5 years	2–5 years	0–23 months
5	Oriented and converses	Appropriate words and phrases	Smiles, coos appropriately
4	Disoriented and converses	Inappropriate words	Cries, consolable
3	Inappropriate words	Persistent cries or screams	Persistent inappropriate crying or screaming
2	Incomprehensible sounds	Grunts	Grunts, agitated or restless
1	No response	No response	No response

Note: A score of 9 or more rules out coma whereas a score of less than 7 confirms coma. Most subjects scoring 8 are too having coma.

Box 28.30 Causes of coma

- **Predominantly CNS causes:**
 - Meningitis
 - Encephalitis
 - Head injury
 - Brain abscess
 - Midline cerebral tumors
 - Subdural empyema
 - Intracranial hemorrhage—subarachnoid hemorrhage.
- **Extra-CNS causes:**
 - Metabolic—diabetic ketoacidosis, hypoglycemia, hepatic encephalopathy, uremia
 - Encephalopathy—typhoid
 - Infections—sepsis, cerebral malaria
 - Dehydrations/dyselectrolytemia—water intoxication, hypernatremia, hyponatremia
 - Postictal
 - Thromboembolism—stroke
 - Hypertension
 - Shock
 - **Thermal injury**—hyperpyrexia, febrile encephalopathy
 - **Poisoning**—narcotics like barbiturates, alcohol, toxins

Abbreviation: CNS, central nervous system.

- **Slow and deep:** Raised ICP, CNS infection or after a convulsive episode
- **Ataxic:** Damage to medulla; respiratory arrest usually follows

Box 28.31 AEIOU—a mnemonic for causes of coma

- A** Acidosis
 - Accidents
 - Alcohol
- E** Epilepsy
 - Encephalitis
 - Encephalopathy
 - Electrolyte imbalance
- I** Injury
 - Intoxication
 - Insulin shock
- O** Oxygen deprivation
 - Overdose of opiates, etc.
- U** Uremia.

Box 28.32 Emergency measures in coma

- Ensure a clear airway
- Consider oxygen administration or tracheostomy
- Maintain clear airway by suction and mouth gag or oral airway
- Start IV drip to administer fluids and to restore acid-base and electrolyte balance
- Consider giving, blood transfusion in case of existing or imminent shock
- Control convulsions, if present
- Control high fever, if present
- Put Ryle tube in order to empty stomach contents and/or to examine these, and to prevent occurrence of abdominal distention
- Take steps to lower the raised ICP
- Consider giving an antidote for narcotic overdose.

Abbreviations: IV, intravenous; ICP, intracranial pressure.

- **Slow, shallow and periodic:** Narcotics
 - **Acetone in breath:** Diabetic acidosis
 - **Foul breath:** Uremia
 - **Blowing out of one cheek:** Ipsilateral facial paralysis
 - **Deep, rapid, gasping:** Acidosis.
 - Pattern of pupil responses:
 - **Widely dilated, fixed:** Third nerve paralysis resulting from tentorial herniation
 - **Widely dilated, but reactive:** Postictal state or deep plane of anesthesia
 - Pinpoint drug intoxication (opiates, barbiturates) or brainstem involvement
 - **Unilateral dilated, fixed:** An expanding lesion on the same side (it may well be a false localizing sign)
 - **Midposition fixed:** Involvement of midbrain level
 - **Roving nonconjugate deviation:** Light plane of anesthesia
 - **Conjugate deviation:** Cerebral lesion of same side or an irritative process on the opposite side
 - **Nystagmoid movement:** Posterior fossa lesion on same side.
 - **Doll's eye phenomenon:** Turn the head briskly from side to side while patient's eyes are open. You would notice that the eyes move conjugately to the opposite side. The reflex (also called **oculocephalic response**) is depressed if the lesion is at the level of midbrain. It is entirely absent if the lesion is below this level. The reflex needs 3rd, 4th and vestibular nerves intact.
 - **Head and body:** Quickly examine for injury marks or evidence of ingestion of poisonous agents.
 - **Fever:** Hypothermia indicates possibility of barbiturate or alcohol intoxication or shock. High fever suggests acute infection. Do not forget that it may be seen in toxic encephalopathies, heat stroke, intracranial hemorrhage or postictal state.
 - **Neck rigidity:** It suggests meningitis. Subarachnoid hemorrhage or herniation of cerebral tonsils may also manifest with nuchal rigidity. However, remember that it may be absent in a comatose child despite his having been suffering from one of these disorders.
 - **Limbs:** Failure to move one side or asymmetrical movements suggest paralysis. In hemiplegia, the paretic leg lies in external rotation and moves less than the normal leg, spontaneously as also in response to painful stimuli. When lifted and allowed to fall back, it drops limply.
- Decerebrate posturing**, characterized by arms which are flexed over the chest, hands which are fisted, and legs which are extended, suggests diffuse cerebral cortex lesion. **Decorticate posturing**, characterized by rigid extension and pronation of legs, as such or in response to pain, suggests midbrain lesion. Unilateral decerebrate posturing, often accompanied by contralateral third nerve palsy is usually a sign of tentorial herniation.
- **Reflexes:** Absence of corneal reflex or tonic neck reflex suggests severe brain damage. A consistently positive Babinski sign may be of value.
 - **Fundoscopy:** Early signs of raised ICP are absence of venous pulsations and distention of retinal veins. Preretinal hemorrhages suggest subarachnoid or subdural hemorrhage. Since papilloedema takes 24–48 hours to manifest, its absence does not mean RIP is ruled out.
 - Focal signs in relation to raised ICP:
 - **Focal signs with raised intracranial pressure:**
 - **Trauma:** Subdural, epidural or intracerebral hemorrhage; subdural contusion
 - Intracranial tumor
 - **CNS infection:** Brain abscess, subdural empyema, encephalitis
 - **Vascular lesions:** Arteriovenous malformations.
 - **Focal signs with normal intracranial pressure:**
 - **Vascular lesion:** Cerebral artery occlusion
 - **CNS infection:** Encephalitis
 - **Trauma:** Cerebral confusion
 - **Epilepsy:** Postictal state with Todd paralysis.
 - **Raised intracranial pressure with absent focal signs:**
 - **Metabolic encephalopathy:** Lead poisoning, water intoxication, Reye syndrome, severe anoxia
 - **CNS infection:** Meningitis, encephalitis
 - **Trauma:** Subdural hemorrhage in infants, subarachnoid hemorrhage
 - Intracranial tumors
 - Hydrocephalus.
 - **Normal intracranial pressure and no focal signs:**
 - **Metabolic encephalopathies:** Most of them

- Drug intoxication
- **CNS infection:** Meningitis, encephalitis
- **Trauma:** Concussion
- **Epilepsy:** Postictal state.

Investigations

■ Urine examination

- Acetonuria and glycosuria—diabetes, sometimes lead encephalopathy, salicylism or cerebrovascular accident
- Albuminuria—uremic coma, lead and other heavy metal poisoning or high fever
- Bilirubinuria—hepatic failure (hepatic coma from viral hepatitis or Reye syndrome)
- A positive ferric chloride test—phenothiazine poisoning, salicylism.

■ Blood examination

- High blood glucose—diabetes
- Low blood sugar—hypoglycemia, Reye syndrome
- Low CO₂ and chlorides—acidosis
- High blood urea nitrogen (BUN)—uremia
- High liver enzymes and ammonia with low bilirubin—Reye syndrome.

■ Lumbar puncture

- High pressure—intracranial infections, space-occupying lesions
- High proteins—meningitis
- High cell count with predominance of polymorphs—pyogenic meningitis
- High cell count with predominance of lymphocytes—tuberculous meningitis
- Nearly normal picture—encephalitis.

■ Head imaging

- CT scan for RIP, intracranial hemorrhage, infarcts, brain tumor, hydrocephalus, etc.

Management

- Once emergency treatment has been instituted and the diagnosis arrived, the specific treatment is of the underlying cause of coma.
- Keep vigilance during treatment.
- The continuous reassessment may indicate need for a change in the treatment at a later stage or minor alterations from time to time. For instance, it is a practice to substitute nasogastric feeding for IV drip, if coma is prolonged. Bladder, may, at some point, need catheterization.
- There is no place for prophylactic antibiotics in the management of coma.

NEURODEGENERATIVE DISORDERS

(Degenerative Brain Disorders)

Definition

These disorders are characterized by progressive loss of intellectual, motor and sensory functions with waxing and waning of manifestations over a prolonged period and no effective therapy.

Box 28.33

Classification of degenerative brain disorders according to area of brain principally involved

Gray matter involvement

- With storage
 - Infantile Gaucher disease
 - Niemann-Pick disease
 - Farber disease
 - Tay-Sach disease
 - Cerebromacular degeneration
 - Generalized gangliosidosis
- Without storage
 - Kinky hair (Menke's) disease
 - Subacute sclerosing panencephalitis (SSPE)
 - Leigh disease
 - Alper disease

White matter involvement

- Leukodystrophies
 - Metachromatic leukodystrophy
 - Cerebroside lipidosis
 - Sudanophilic leukodystrophy
 - Canavan disease
- Demyelinating
 - Schilder disease
 - Neuromyelitis optica
 - Multiple sclerosis

Systemic degeneration

- Cerebellar/Spinocerebellar
 - Friedreich ataxia
 - Refsum disease
 - Ataxia-telangiectasia
 - Bassen-Kornzweig syndrome
- Basal ganglia
 - Hepatolenticular degeneration
 - Huntington chorea
 - Dystonia musculorum deformans
 - Hallervorden-Spatz disease.

Classification

Box 28.33 gives the classification based on area of principle involvement.

Clinical Features

- The dominant early manifestations in gray matter involvement include dementia and convulsions. Eventually, however, the whole nervous system suffers.
- The dominant early manifestations in white matter involvement include deterioration in motor function in the form of spasticity, hypotonia or ataxia. With progression of the disease, the whole nervous system suffers.
- The end-stage clinical picture in all degenerative disorders is more or less similar, the patient losing all intellectual and voluntary motor functions and becoming helpless.

Salient Features of Specific Neurodegenerative Disorders

Subacute Sclerosing Panencephalitis

(Dawson Encephalitis)

Subacute sclerosing panencephalitis (SSPE) manifests several months to years after the primary infection with

measles. The peak incidence occurs at 5–15 years though it has been reported in subjects aged 6 months to 30 years. Manifestations include personality changes followed by generalized myoclonic jerks and, at times, grand mal seizures. With progression of the disease, the patient becomes demented, rigid and bedridden. The disease invariably proves fatal within 2 years.

Cerebrospinal fluid is normal except for high gamma globulin levels and measles antibody titer of more than 1 in 128 by complement fixation method. Electroencephalogram shows regularly repeated bursts of generalized high voltage slow wave complexes.

CT scan or MRI reveals variable cortical atrophy, ventricular enlargement and focal or multifocal low density lesions in white matter in established disease.

Brain biopsy (no longer required for diagnosis) shows perivascular lymphocytic infiltration, inclusion bodies in neurons and glial cells, loss of neuronal cells, gliosis and, at times, growth of measles virus from cerebral tissue. Management is by and large symptomatic and supportive. Inosiplex, 100 mg/kg/day in divided doses, causes some clinical improvement and prolonged survival.

Rett Syndrome

Occurring exclusively in females, it is characterized by regression of motor milestones and language after 1 year of age, ataxic gait or fine tremors of hands, sighing respiration with intermittent apneic spells, repetitive hand-wringing movements and autistic behavior. Associated features include generalized tonic-clonic seizures, feeding problems, and poor weight gain. Endorphin level in CSF is elevated. Treatment with anticonvulsants controls seizures and with naltrexone, an opiate-receptor agent, improves apnea and behavioral problems in a proportion of cases.

Kinky Hair (Menkes) Disease

A sex-linked recessive disorder of copper metabolism, is characterized by poor weight gain, proneness to infection and, later, hair becoming sparse and brittle, and myoclonic seizures. X-ray shows scurvy-like picture in long bones. Serum copper and ceruloplasmin levels are reduced. Despite parenteral copper therapy, gross cerebral and arterial changes prove fatal in infancy per se.

Metachromatic Leukodystrophy

This the most common of the leukodystrophies, is an autosomal disorder due to deficiency of arylsulfatase A (ASA) in brain and other tissues. Manifestations, appearing at about 1 year of age, include gait disturbances, spasticity, hyperreflexia, extensor plantars, brisk tendon reflexes with the exception of ankle jerk which may be sluggish or absent, flaccid weakness and wasting of muscles and, eventually, dementia and immobility. Most patients are dead by the age of 10 years. Prenatal diagnosis by amniocentesis is possible.

Demyelinating Diseases

These are characterized by breakdown of myelin in CNS only and are supposed to be secondary to an autoimmune or viral etiology. Three types are known:

1. **Schilder's disease** manifests with cortical blindness, optic neuritis, cortical deafness, spastic hemiplegia or paraparesis, aphasia, convulsions, and, at a later stage, dementia and coma. RIP occurs only occasionally. Partial remission may occur rarely.
2. **Multiple sclerosis** manifests by cerebellar ataxia, spasticity, retrobulbar optic neuritis and atrophy, diplopia, and blindness. Course is relapsing and IQ is preserved till late. Therapeutic measures include short courses of ACTH, physiotherapy, treatment of UTI and bladder care. Symptom free remission for many years is known.
3. **Neuromyelitis optica (Devic disease)** manifests with eye pain and blindness followed in some days by spinal cord involvement in the form of first lower motor neuron and then upper motor neuron paralysis of the legs. Upper level of sensory involvement is in thoracic area.

Fundoscopy may show swelling and hyperemia of disk, distention of retinal veins and peripapillary hemorrhages. A 5–7 days course of dexamethasone (high doses) is indicated. Vision usually returns but some paraparesis persists.

Friedreich Ataxia

The most common of the spinocerebellar degenerations, it usually has autosomal recessive inheritance. Manifestations include ataxia with skeletal defects such as pes cavus (high-arched foot), hammer toes and scoliosis, dysarthria, intention tremors, nystagmus, extensor plantars, loss of tendon reflexes, muscle wasting, and cardiomegaly. No effective treatment is available. Death usually follows congestive cardiac failure (CCF).

Hepatolenticular Degeneration (Wilson Disease)

An autosomal recessive disorder of copper metabolism, it is characterized by triad of cirrhosis, neurological manifestations and Kayser-Fleischer rings. Hepatomegaly, due to excessive accumulation of copper is the earliest manifestation. Splenomegaly, jaundice and anorexia follow it. Edema, ascites or gastrointestinal bleeding occurs sooner or later.

Neurologic manifestations include proximal tremors of outstretched arms and wrists (wing-beating tremors), dysarthria and dystonia at an advanced stage. Serum copper and ceruloplasmin levels are reduced whereas liver tissue copper exceeds 400 µg/g dry weight.

Therapy comprises of chelating agent (penicillamine), and low copper diet. This has greatly improved prognosis of this otherwise a fatal disease.

NEUROCUTANEOUS SYNDROMES (PHAKOMATOSES)

Neurofibromatosis

It is an autosomal dominant neurocutaneous disorder, it is of two types:



Fig 28.28: Café-au-lait spot. Note the darkish large skin lesion in neurofibromatosis type 1 (NF-1). The child had axillary freckling and mild mental retardation (IQ 60). Her elder brother too suffered from NF-1.

1. **Von Recklinghausen disease (peripheral neurofibromatosis {NF-1}):** It is characterized by at least two of the following features:
 - Café-au-lait spots (irregular hyperpigmented areas— more than 6 spots, each of at least 5 mm diameter before puberty and 15 mm diameter after puberty) (Fig. 28.28).
 - Axillary/inguinal freckling (Crowe sign) and speckled hyperpigmentation.
 - Neurofibromas involving skin, subcutaneous tissue, oral mucosa, musculoskeletal system, GIT, eyes, and CNS leading to a variety of manifestations.
 - Optic glioma.
 - Lisch nodules (two or more), dysplasia of sphenoid bone or thinning of long bone cortex.
 - The existence of disease in a first degree relative. Incidence of congenital malformations and neural tumors, such as pheochromocytoma, meningioma and glioma of optic chiasma and nerve, and sarcomas is increased. Mental retardation, though mild, is a common accompaniment.
2. **Central neurofibromatosis (NF-2):** Auditory neuroma (unilateral or bilateral), meningioma, lenticular opacity (posterior subcapsular).

Tuberous Sclerosis (Bourneville Disease)

This is an autosomal dominant disorder involving multiple systems. Clinical manifestations include mental retardation, epilepsy and multiple cutaneous stigmata. Two types of typical skin lesions are noteworthy:

1. **Ash leaf lesions:** White hypopigmented ash leaf spots (Fig. 28.29).
2. **Adenoma sebaceum:** Angiofibromas of pink or red color over face (Fig 28.30).

Shagreen patches, subungual and oral fibromas, retinal hamartomas, etc. may too occur. Benign tumors (tubers) are found in such organs as brain (visible as characteristic calcification on skull X-ray), kidneys, fundi (retinal phakomas), heart (rhabdomyoma), bones (areas of sclerosis and rarefaction on X-ray), lungs, liver and spleen. Tuberous sclerosis may cause infantile myoclonic spasms (West syndrome).



Fig. 28.29: Tuberous sclerosis. Note the ash leaf lesions.



Fig. 28.30: Adenoma sebaceum. Note the pinkish neurofibromas over face in a child with tuberous sclerosis.

Sturge-Weber Disease

A nonfamilial disorder, it results from a unilateral congenital capillary hemangioma involving face and neck (facial nevus, involving usually ophthalmic division of trigeminal nerve), mucos membrane, meninges and choroid plexus. Neurologic manifestations include seizures, hemiparesis or hemianopsia, rarely subarachnoid hemorrhage, glaucoma, and railroad-track (tram-track) pattern of calcification on X-ray skull (Fig 28.31).

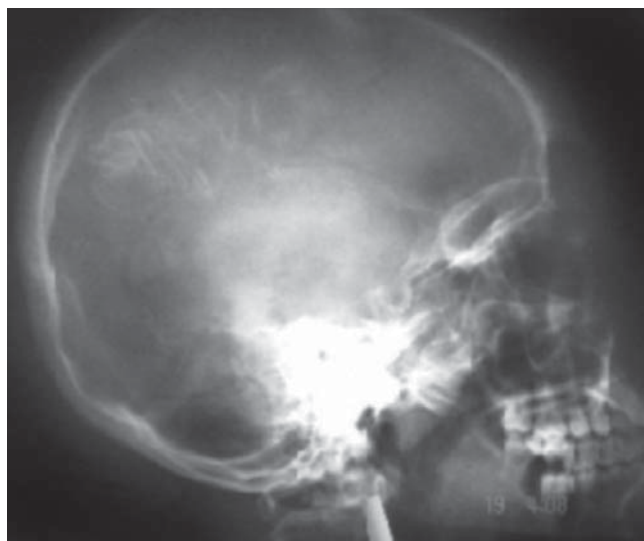


Fig. 28.31: Sturge-Weber syndrome. Note the rail-track (tram-track) calcification in the frontoparietal region in skull X-ray.

Ataxia Telangiectasia

An autosomal recessive disorder comprising of defective embryogenesis, it is characterized by cerebellar ataxia, ocular and cutaneous telangiectasia, chronic sinopulmonary infection, endocrinal abnormalities and immunodeficiency of B and T cell (most frequently immunoglobulin A {IgA} and immunoglobulin E {IgE} deficiency, singly or together).

All subjects demonstrate presence of alpha-fetoprotein, carcinoembryonic antigen. X-ray exposure must be avoided in the subjects with this condition. High chromosomal breaks on chromosome 14 are frequently encountered. Death follows lymphoreticular malignancy with the worsening of the T cell deficiency, or a resistant infection.

von-Hippel-Landau Disease

This disease is characterized by visual loss, spinal cord angiomas, cerebellar and retinal hemangioblastomas, and cystic tumors of kidneys, pancreas and epididymis. Neurological manifestations include RIP, nystagmus and ataxia.

Linear Nevus Syndrome

A sporadic condition, it is characterized by a facial nevus over middle of forehead and nose and neurodevelopmental defects. Usual accompaniments include mental retardation, seizures (generalized myoclonic or focal motor) and focal neurologic signs including hemiparesis and hemianopia (homonymous).

Incontinentia Pigmenti (Bloch-Sulzberger Disease)

An X-linked dominant disorder, lethal to the males, is characterized by multisystem involvement. Neurological manifestations include seizures, developmental delay, microcephaly, spasticity and paralysis.

In addition, there are cutaneous lesions, alopecia, dystrophied nails, skeletal defects, dental anomalies (delayed eruption, conical teeth, and partial anodontia), squint, optic nerve atrophy, cataracts, and retrolenticular masses. One-third patients may end up with blindness. Investigations and management are dictated by the noncutaneous abnormalities rather than skin lesions, which are benign and show regression during adulthood.

Multiple Choice Questions

- Spot the wrong entry:
 - Presence of 2 or more soft neurological signs suggests a neurological dysfunction
 - Psychometric tests are useful in evaluating cognitive ability and intelligence of a suspected case of mental retardation
 - Spina bifida occulta is the most frequent and most benign neural tube defect
 - Bell palsy is a lower motor neuron lesion
 - Pseudo tumor cerebri is always a benign illness
- All of the following entries about mental retardation are correct, except:
 - An IQ less than 20 points to profound mental retardation
 - Severe and profound mental retardation are custodial, moderate and is trainable and mild educable
 - Reversible mental retardation comprises of conditions such as phenylketonuria, congenital hypothyroidism, severe protein-energy malnutrition
 - Neurodevelopmental problems such as autism and spectrum disorder are true mental retardation
 - Avoidance of consanguineous marriages is an important step towards prevention of mental retardation
- Scrotal tongue is a feature of:
 - Congenital hypothyroidism
 - Turner syndrome
 - Down syndrome
 - Congenital rubella syndrome
 - Gaucher disease
- Usual comorbidities of cerebral palsy include all of the following, except:
 - Epilepsy
 - Diarrhea
 - Various paresis/paralysis
 - Mental retardation
 - Incontinence
- Usual endocrine sequelae of meningitis include each of the following, except:
 - Diabetes mellitus
 - Diabetes insipidus
 - Precocious puberty
 - Obesity
 - Mental retardation

Answers

1. E 2. D 3. C 4. B 5. A

Clinical Problem-solving

Review 1

A 5-year-old healthy child suddenly develops severe truncal ataxia with rapid deterioration in gait. A month back he along with his mother had suffered from influenza (documented by positive test) with complete recovery in a week's time. Romberg sign is negative.

1. What according to you should be the diagnosis?
2. How to confirm the clinical impression?
3. Can CSF be of any help?
4. What is the projected outcome?

Review 2

A 13-year-old boy, a known case of achondroplasia, presents with spastic paralysis of abdomen and lower limb muscles, among several superficial injuries following an accident. The diagnosis of traumatic paraplegia is made.

1. Identify the site of the lesion.
2. Which abdominal muscles are involved?
3. What should be the broad therapeutic approach in this boy?

Answers

Review 1

1. Acute cerebellar ataxia following influenza a few weeks back.
2. Acute cerebellar ataxia is purely a clinical diagnosis reached after exclusion of other causes of ataxia.
3. Not much. It is usually normal in acute cerebellar ataxia. Only in 1/4th cases, slight pleocytosis is noticed.
4. Acute cerebellar ataxia is a self-limiting condition. In mild cases, ataxia clears in a week or so. In severe cases, complete recovery may take a couple of months.

Review 2

1. In view of spastic paralysis of abdomen together with lower limb muscles, the level of lesion should be T₆.
2. Intercostals, rectus abdominalis (both upper and lower) and oblique abdominalis.
3. A good nursing care along with physiotherapy (first passive and then active) are important initially. Eventually, the patient may need surgical intervention as well.

FURTHER READING

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BASICS OF GASTROINTESTINAL TRACT

The term, **gastrointestinal tract (GIT)**, refers to the alimentary tract extending from the mouth to the anus. It is divided into mouth, oropharynx, esophagus, stomach, small intestine (jejunum and ileum) and large intestine (colon).

On ingestion of food by the mouth, it is moved by the oropharynx into the esophagus. The latter acts as a conduit for transfer of food to the stomach, where it is stored and mixed prior to its controlled passage into the small intestine, where it is digested and absorbed. Then, it moves to large intestine where salts and water are conserved prior to excretion as feces.

Undoubtedly, the normal GIT function is the net result of combined action of many functional systems. If there is a breakdown of any one, intestinal function will be disturbed. For instance, diarrhea develops when there is an enhanced overload of fluids from small intestines into the colon following maldigestion or active secretion, or when the absorptive capacity of the colon is compromised by disease. A defect of intestinal mucosal immunity may lead to recurrent enteric infections. Intestinal obstruction follows loss of normal intestinal motility. An insult to the digestive or absorptive capacity of the GIT may cause digestive and abdominal complaints, failure to thrive (FTT) and even weight loss. Diseases elsewhere may also present with manifestations attributable to the GIT.

DIAGNOSTIC WORK-UP FOR GASTROINTESTINAL DISORDERS

Clinical Work-up

A good history and physical examination together with skillful interpretation of the common symptoms and signs *See Chapter 2 (Pediatric History-taking and Clinical Examination)* assist in deciding about the various investigations to arrive at the final diagnosis in a child suspected of a gastrointestinal disorder.

Special Investigative Work-up

For esophageal structure and function

- Barium meal studies for defining anatomy of upper GIT and detecting advanced mucosal lesions, e.g. varices and gastroesophageal reflux (GER).
- Endoscopy for varices.
- 24-hour pH monitoring is the most sensitive test for GER.
- Esophagoscopy for esophagitis and mucosal biopsy.

For maldigestion/malabsorption

- Stool examination, including fat globules, reducing substances, pH, and microscopy is advisable. In case of a strong suspicion of intestinal parasitosis, it is advisable to carry stool microscopy by concentration method for at least 3 (preferably 6) consecutive days since ova and cysts frequently pass intermittently. For details, *See Chapter 49 (Pediatric Practical Procedures.)*
- 24-hour stool fat by fat balance studies and chemical examination of stools or by a semiquantitative method termed as **steatocrit**. A daily stool fat of greater than 5 g is considered indicative of steatorrhea.
- D-xylose test consists in measuring excretion of xylose in a 5-hour sample of urine after administering the pentose in a dose of 1 g/kg body weight (BW). An excretion of <20% points to malabsorption. A tolerance test too is available for infants and small children in whom collection of urine sample is quite cumbersome.
- Anti-tissue transglutaminase for celiac disease (CD)
- Lactose tolerance test.
- **Breath test** involving measurement of H⁺.
- **Barium meal follow-through**, employing a non-flocculable medium, may reveal intestinal changes indicative of malabsorption, such as intestinal dilatation, flocculation, and atypical mucosal pattern, plus anatomic defects.
- **Endoscopic gastric or jejunal biopsy**: The jejunal biopsy provides vital histologic details as well as the material for enzymes, disaccharidases, especially, lactase, assay. It may also identify such pathogens as *Giardia lamblia* and *Helicobacter pylori*. Gastric biopsy may be employed for histopathology, culture or rapid urea test for *H. pylori*.
- **Schilling test** measures the vitamin B₁₂ absorption from the gut. It consists in administering a tracer dose of radioactive vitamin B₁₂, after saturating body stores with vitamin B₁₂, and its urinary excretion measured over the next 24 hours. An excretion of < 5% indicates defective absorption from the ileum.
- **Sweat chloride** estimation by iontophoresis, using pilocarpine, is important for assay of the exocrine pancreatic function. A level of >60 mEq/L usually establishes the diagnosis of cystic fibrosis.

DIARRHEAL DISEASES: AN OVERVIEW

Diarrheal diseases rank among the **top three** causes of death in pediatric population of the developing world. Globally, approximately 4–5 million deaths occur as

550 a result of diarrheal diseases every year. Eight out of these 10 deaths are in the first 2 years of life, the most susceptible period for malnutrition. As indicated in Chapter 2 (Pediatric History-taking and physical (Clinical Examination) diarrhea accounts for about 20% of the hospitalized pediatric cases in India.

On an average, a child suffers from around 12 episodes of diarrhea, 4 such episodes occurring during the very infancy (first year). Existence of malnutrition makes the child very much vulnerable to diarrheal disease. It is estimated that incidence of diarrhea in malnourished children is five to seven times higher than in healthy children. Likewise, its severity too is three to four times greater.

By definition, **diarrhea** means passage of three or more loose or watery motions per 24 hours, resulting in excessive loss of fluid and electrolytes in stools. Secretory, osmotic or motility abnormalities, singularly or in combination, form the basis of all diarrheal episodes.

- **Secretory diarrhea** has a tendency to be watery, voluminous and persistent even when no feeding is given orally. It is usually caused by an external or internal secretagogue (cholera toxin, lactase deficiency).
- **Osmotic diarrhea** follows ingestion of a poorly absorbed solute because of an inherent character of the solute (magnesium phosphate, alcohol, sorbitol) or a small bowel defect (lactose in lactase deficiency in brush-border). It tends to be watery and acidic with reducing substances.
- **Motility diarrhea** is associated with increased (irritable bowel syndrome) or delayed motility (intestinal pseudo-obstruction).
- **Acute diarrhea** refers to diarrhea that begins acutely and terminates within a week or so, only a small proportion of cases passes to the second week or even beyond.
- **Chronic diarrhea** refers to diarrhea beyond 2 weeks. The term is best reserved for cases with an obvious malabsorptive disorder or, less frequently, an underlying organic disease without obvious malabsorption.
- The term **persistent diarrhea** denotes an episode of acute diarrhea, presumably of infective origin, that lasts for 2 weeks or more.
- The term **intractable diarrhea of infancy** should be reserved for cases that have onset of protracted diarrhea before the age of 3 months. These infants start as an infective diarrhea, become dehydrated and wasted and have high mortality. They need emergency treatment.

ACUTE DIARRHEA

(Acute Gastroenteritis)

Acute diarrhea, often accompanied by gastritis manifesting as vomiting, is called **acute gastroenteritis**. It is a leading cause of morbidity and mortality in pediatric practice. The incidence and mortality are especially high in infancy,

Box 29.1

Etiology of acute diarrhea

• Enteric infections

- **Bacteria:** *Escherichia coli*, *Shigella*, *Salmonella*, *Staphylococcus*, *Cholera vibrio*, *Yersinia enterocolitica*, *Campylobacter jejuni*, *Clostridium difficile*, *Aeromonas hydrophilia*, *Vibrio parahemolyticus*, *Plesiomonas shigelloides*
- **Viruses:** Rotavirus, Norwalk and allied viruses, Enterovirus. Influenza virus, Measles virus
- **Parasites:** *Entameba histolytica*, *Giardia lamblia*, *Cryptosporidium*, *Cyclospora cayetanensis*, *Isospora*, *Hymenolepis nana*, *Trichuris trichiura*, malarial parasite
- **Fungi:** *Candida albicans*
- **Parenteral:** URI, otitis media, tonsillitis, pneumonia, urinary tract infection
- **Drugs:** Antibiotics
- **Dietetic/Nutritional:** Overfeeding, starvation, food allergy, food poisoning
- Nonspecific.

Abbreviation: URI, upper respiratory infection.

more so in the presence of malnutrition and erratic feeding practices.

According to a conservative estimate, almost 500 million children suffer from acute diarrhea annually. Of them, 5 million die every year. In India alone, nearly 1.5 million children die due to acute diarrhea every year.

Etiology

Box 29.1 lists various causes of acute diarrhea in infancy and childhood. This acute diarrhea, mostly infectious in origin in pediatric practice, is borne out by the following points:

- Magnitude of diarrhea prevalence is directly proportional to sanitary and personal hygiene standards of the community.
- Acute diarrhea in the community behaves on the same lines as other infectious diseases.
- Infants and children are more frequently and more severely affected than older people, indicating poor immunity in the former.

Viral Diarrhea

Recent evidence has indicated that viruses, such as rotavirus and Norwalk and Norwalk-like agents, are responsible for majority of the acute diarrhea in infants and young children.

Rotavirus, also termed as **gastroenteritis virus (GEV)**, is the most frequently encountered virus in diarrheal stools of children. Four established serotypes of rotavirus account for 20–40% of acute diarrhea. Age 9–12 months appears to show the peak incidence. Excepting newborns, it has been observed to have a predilection for winter and dry months in the Indian subcontinent. Transmission is by feco-oral route.

The virus causes reversible patchy villous atrophy and loss in the absorptive capacity of the intestinal mucosa in a cephalocaudal direction. A marginal reduction in disaccharidases with some reduction in carbohydrate absorption is usually present such Brush border enzymes

such as alkaline phosphatase, sucrase and trehalase are also reduced. The small intestinal morphology and function revert to normal within 2–3 weeks. Incubation period is usually < 48 hours (range 1–7 days). The average duration of illness is 5–7 days.

An important clinical feature of rotavirus diarrhea is the vomiting that usually precedes the onset of watery motions. About 30–50% cases show slight fever, 25% mucus in stools and, just an occasional case, blood in stools. It is responsible for 10–20% of acute diarrheal cases.

Norwalk and Norwalk-like agents, are also associated with outbreaks of generally mild gastroenteritis occurring in school, community and family settings. Notwithstanding minor histological insult to small intestinal mucosa, brush border enzymes are reduced.

The incubation period is around 48 hours. The attack is usually mild and self-limiting, lasting 12–24 hours in a majority of the cases.

Vomiting, abdominal pain, anorexia, headache, myalgia and malaise are important features of diarrhea, secondary to this group of viruses. Other viruses incriminated in the etiology of diarrhea include *Hawaii virus*, *adenovirus*, *astroid virus*, *calici-virus*, *coronavirus*, *enterovirus* and *minirota-virus*.

Bacterial Diarrhea

This constitutes the next major group. The most dominant pathogen in this category is *Escherichia coli*. *Diarrheagenic E. coli* have five classes—*enteropathogenic E. coli* (EPEC), *enterotoxigenic E. coli* (ETEC), *enterohemorrhagic E. coli* (EHEC), *entero-adherent E. coli* (EAEC) and *enteroinvasive E. coli* (EIEC). ETEC are notorious for causing dehydrating diarrhea in developing countries. EIEC causes shigellosis-like illness. EPEC is responsible for prolonged diarrhea (non-bloody) with mucus and at times, pyrexia. EHEC is characterized by abdominal pain and diarrhea which soon becomes bloody (hemorrhagic colitis) as in case of shigellosis. This is called **EIEC illness**. Risk of developing hemolytic-uremic syndrome in EHEC diarrhea with pyrexia is enhanced. EAEC usually causes dehydrating diarrhea which often becomes prolonged as in case of EPEC.

***Vibrio cholerae* 01 and 0139**, contrary to the widely-held belief, cause severe watery diarrhea and vomiting only in a minority of the children. In most cases, the infection is mild with minor or no symptoms.

Shigella, *Campylobacter jejuni* and *nontyphoidal Salmonella* account for about 10%, 12% and 3% of acute diarrhea cases, respectively. These bacteria, along with EIEC may cause damage to the mucosa of distal ileum and colon through their toxins, leading to formation of ulcers as also mucosal secretion of water and electrolytes, and dysentery.

Parasitic Diarrhea

Giardia lamblia is an important cause of recurrent diarrhea. *Entameba histolytica* is encountered relatively less frequently in infants and children, *Hymenolepis nana* (dwarf tapeworm) is common in some pockets only. These

three pathogens may infrequently cause even dysentery-like manifestations.

Cryptosporidium, a coccidian protozoan parasite, typically causes watery diarrhea, varying from mild to severe, together with crampy epigastric pain, vomiting, anorexia, malaise and loss of weight. In immunodeficiency states (human immunodeficiency virus {HIV} infection, congenital hypogammaglobulinemia, immunosuppressant therapy in hematogenous malignancies), cryptosporidiosis may cause acute diarrhea that tends to become persistent diarrhea, frequently ending up fatally.

Pathogenesis

Diarrhea: Modus Operandi of Development

The delicate balance in the ecology of the GIT needs to be broken down by one of the two situations in order that diarrhea occurs:

- The conditions in which the defense weakens, say malnutrition (both primary and secondary), immunologic disorders, etc. so that even commensal organisms with weak virulence, or opportunist organisms overpower and cause diarrhea
 - The known pathogens overcome the natural defense.
- The pathogenic organisms produce diarrhea by one or more of the mechanisms (Box 29.2).

Secretory and Osmotic Diarrhea

Secretory diarrhea results from activation of intracellular mediators like cyclic adenosine monophosphate (cholera, heat-labile *E. coli*, *Shigella*, *Salmonella*, *Campylobacter jejuni*, *Pseudomonas aeruginosa*), hormones (vasoactive intestinal peptides, gastrin, secretin, anion), surfactants (bile acids, ricinoleic acid), cyclic guanosine monophosphate (heat-stable *E. coli*, *Yersinia enterocolitica*), and intracellular calcium (*Clostridium difficile*, acetyl choline, serotonin, bradykinin).

Osmotic diarrhea results from excessive intake of carbonated drinks or nonabsorbable solutes (sorbitol, lactulose, magnesium hydroxide). These concentrated substances (say, lactose, lactulose) are not absorbed from the gut. They pull water from intestinal wall into stools. Such a diarrhea subsides on fasting.

Box 29.2

Modus operandi of production of diarrhea by pathogens

- Adhesion to the intestinal mucosal wall, e.g. *enteropathogenic E. coli* (EPEC) which are further categorized as class I EPEC (showing localized adherence) and class II EPEC (showing diffuse adherence).
- Elaboration of an exotoxin, (secretory diarrhea), e.g. *rotavirus*, *enterotoxigenic E. coli* (ETEC), *Vibrio cholerae*, *Aeromonas hydrophila*, *Plesiomonas shigelloides*, causes excessive secretions. Fasting has no effect.
- Mucosal invasion (exudative diarrhea), e.g. *enteroinvasive E. coli* (EIEC), *Shigella*, *Salmonella* (*nontyphi*), *Clostridium difficile*, *Campylobacter jejuni*, *Yersinia enterocolitica*, *enteropathogenic E. coli* (EPEC), *rotavirus*, damage and exudative blood. Fasting exerts no effect.

552 Diarrheal Dehydration: Modus operandi

In order to appreciate the modus operandi of diarrheal dehydration and dyselectrolytemia, it must be noted that diarrheal losses are drawn from extracellular fluid (ECF) compartment constituted by circulating blood, interstitial fluid and secretions. This compartment accounts for the 60% of the BW of the child.

Loss of water from the child's body causes shrinkage in the volume of the ECF compartment. In around one-half cases with excessive sodium loss in stools, hyponatremia develops as a result of fall in serum and ECF sodium levels. Since sodium is the major determinant of osmolality, there results fall in osmolality of ECF, then follows movement of water from ECF to intracellular fluid (ICF) compartment. Further shrinkage of the already shrunk ECF compartment volume becomes inevitable. This is manifested in the form of loss or impairment of skin elasticity.

In a small proportion of cases in which diarrheal dehydration has been treated with fluids containing far too much of sodium, osmotic pressure of ECF becomes high, prompting water in ICF compartment to move to ECF compartment. This is likely to camouflage the existence of severe dehydration which may erroneously be interpreted as mild dehydration. Depletion of ECF compartment leads to reduction in blood volume, causing peripheral circulatory failure and oliguria or anuria. Loss of potassium in stools leads to hypokalemia, causing abdominal distention, hypotonia and electrocardiogram (ECG) changes in the form of ST depression and flat T wave. Loss of bicarbonate in stools leads to acidemia, causing acidotic respiration (Kussmaul breathing) which is characteristically deep and rapid.

Clinical Features

Clinical picture varies in mild, moderate and severe cases (Tables 29.1 and Fig. 29.1).

- **Mild diarrhea:** In mild cases, onset is usually insidious with two to five motions, which may be loose, green, offensive and contain mucus and milk curds. The volume may be small or large. The attack usually subsides in a day or two without any remarkable constitutional manifestations or dehydrations.



Fig. 29.1: Severe diarrheal dehydration. Note the characteristic features, including moribund state with shock, acidosis and anuria. Oral rehydration solution (ORS), hailed as the most important medical advance of the 20th century, has the potential of saving 10,000 children each day—the child population that could otherwise die from diarrheal dehydration.

- **Moderate diarrhea:** The number of motions is ten or more and constitutional symptoms like fever, irritability, anorexia and vomiting are usually present. Mild dehydration (3–5%) is associated.
- **Severe diarrhea:** Here the child passes 'too many' loose motions and has severe vomiting to the extent that nothing is retained and the oral intake becomes virtually impracticable. Such cases are most often characterized by sudden, rather than gradual, onset. They may have marked constitutional symptoms. Moderate (5–10%) to severe (> 10%) dehydration further aggravates the clinical picture.

Table 29.2 summarizes the clinical picture seen in different grades of dehydration.

Manifestations secondary to central nervous system (CNS) disturbances are prominent in all types of severe dehydration (Table 29.3). Hypertonic dehydration has more of these. Early irritability, alternating with apathy, may progress to restlessness, cloudiness or consciousness, delirium or stupor, lethargy and coma. Convulsions may occur at any stage. The high viscosity of blood may cause as serious a complication as cerebral thrombosis.

In addition to cerebral thrombosis, conditions that may cause seizures in acute diarrhea or AGE include marked hyponatremia, rapid correction of hypernatremia,

Table 29.1: Clinical features of viral versus bacterial diarrhea

Features	Viral diarrhea	Bacterial diarrhea	
		Noninvasive	Invasive
Character of motions	Watery	Watery or semisolid with mucus, but no blood	Semisolid, small amount, very frequent, with mucus and blood
Vomiting	Severe	Only slight	Moderate
Pyrexia	Slight	Nil	Moderate to high
URI	Usually present	Nil	Nil
Seizures	Nil	Nil	Occasionally
Toxemia	Nil	Nil	Slight
Stool microscopy	Moderate pus cells	NAD	Moderate pus and red cells

Abbreviations: NAD, nothing abnormal detected; URI, upper respiratory infection.

Table 29.2: Clinical picture of different grades of dehydration

Grade of dehydration	Estimated fluid loss	Clinical picture
Mild (3–5% weight loss)	<50 mL/kg	Irritability or drowsiness; pallor; somewhat sunken eyes.
Moderate (6–10% weight loss)	50–100 mL/kg	Sick-looking child, pallor, depressed anterior fontanel, sunken eyes, dry mucous membrane, dry and inelastic skin.
Severe (>10% weight loss)	>100 mL/kg	Signs of superimposed shock (coma, limpness, pallor, cold-clammy skin, thin, rapid or almost impalpable peripheral pulses), metabolic acidosis, oliguria/anuria.

Table 29.3: Clinical picture in isotonic, hypotonic and hypertonic dehydration

Criteria	Isotonic	Hypertonic	Hypotonic
Skin color	Gray	Gray	Gray
Temperature	Cold	Cold or hot	Cold
Turgor	Poor	Fair	Very poor
Feel	Dry	Thickened	Clammy (moist)
Mucous membrane	Dry	Parched	Slightly moist
Eyes	Sunken and soft	Sunken	Sunken and soft
Anterior fontanel	Depressed	Depressed	Depressed
Sensorium	Drowsy	Very irritable	Comatose
Pulse	Rapid	Moderately rapid	Rapid
Blood pressure	Low	Moderately low	Very low

hypocalcemia, hypomagnesemia, encephalitis and shigellosis. Table 29.4 summarizes the clinical picture seen in certain special situations.

Clinical Assessment of Diarrheal Dehydration

Since laboratory investigations are most often not available, it is advisable to make the best use of one's clinical knowledge in evaluating the grades and type of dehydration (Table 29.5).

Management

Conventional Rehydration Therapy

Replacement of the fluids as soon as possible is the sheet-anchor of management of acute diarrhea:

- **Oral rehydration therapy (ORT)**, is described in detail later in this very chapter, is ideal for mild dehydration and a majority of the children with moderate dehydration. Current recommendation in infants and children is reduced osmolarity oral rehydration salts (ORS) (osmolarity 245 mOsm/L instead of 311 mOsm/L in WHO standard ORS). A

Table 29.4: Clinical picture in certain special situations

Conditions	Physical signs
Acidosis	Breathing increased in depth and rate
Alkalosis	Breathing decreased in depth and rate; latent or manifest tetany
Hypokalemia	Abdominal distention, paralytic ileus hypotonia, hyporeflexia; mental apathy; ECG changes
Hyperkalemia	Fibrillation or paralysis of skeletal muscles; ECG changes
Hypocalcemia	Tetany; paralytic ileus
Hypercalcemia	Hypotonia; fecal masses
Hypomagnesemia	Tetany; muscular twitching
Hypermagnesemia	CNS depression; hyporeflexia

Abbreviations: ECG, electrocardiogram; CNS, central nervous system.

home-made electrolyte solution (HES) may also be used. There are distinct advantages in using a cereal-based solution, such as rice-water electrolyte solution (RWES), especially since it has a better tolerance and provides greater energy. Each motion must be followed by replacement with an equal amount of ORS. Breastfeeding must not be discontinued. In fact, it potentiates the usefulness of ORT.

- **Intravenous fluid therapy** is indicated in cases with severe dehydration (Fig. 29.2) and those who fail to retain ORS persistently. It consists of deficit and maintenance therapy.
- **Deficit therapy:** A particular grade of dehydration, moderate for instance, may mean variation from 5 to 10% weight loss. It is, therefore, rather unrealistic to administer the same amount of fluid to all such children. Table 29.6 gives a modification of a popular scoring system. It has yielded gratifying results in ours as well as others' experience in managing dehydrated infants and children.

The deficit therapy is obtained by the following:

$$\text{Score} \times \text{weight in kg} \times 10$$

Thus, an 18-month-old, weighing 10 kg and scoring 8 points (8% dehydration or weight loss) requires $8 \times 10 \times 10 = 800$ mL of fluids to cover the deficit as a result of dehydration.

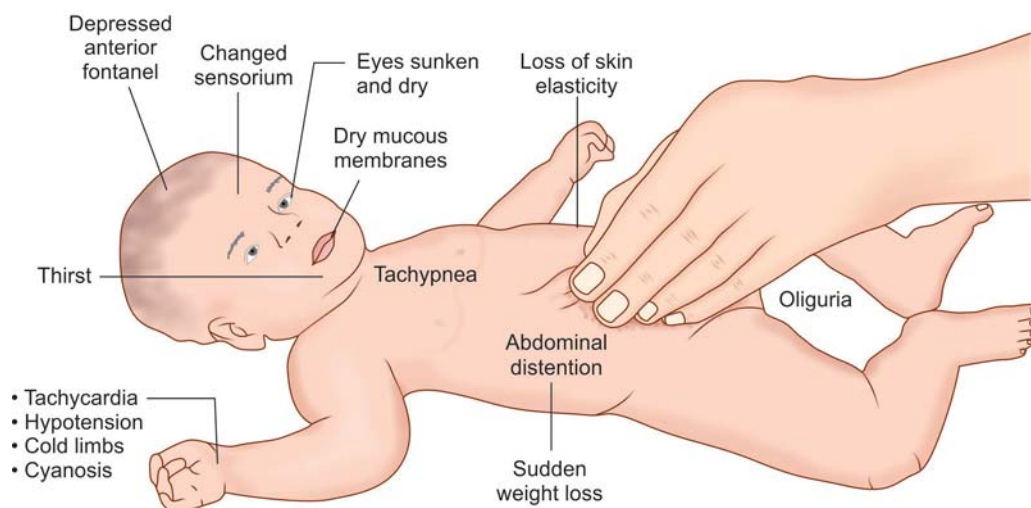
- **Maintenance therapy:** It is best calculated as already outlined in Chapter 16 (Fluid, Electrolytes and Acid-base Balance and Disturbances). Thus, again taking up the just-cited example, this 18-month-old needs $125 \times 10 = 1250$ mL of fluids/24 hours (Table 29.7).
- **Plan of therapy:** Different centers employ different plans. The following lines of administering the fluids are generally favored*:
 - **Initial therapy:** Of the total fluids calculated for 24 hours, one-fifth is given rapidly in the form of Ringer lactate in 2.5 or 5% glucose during the first 1–2 hours**.

* The vast majority of pediatric dehydration in India is 'isotonic'. The regimen is, therefore, by far the best in our set-up.

** To determine number of drops per minute, apply this equation: No. of drops/minute = mL to be given in one hour/3

Table 29.5: Assessment of diarrheal dehydration as per the World Health Organization

Area of clinical observation	Actual observation(s)		
	No dehydration	Some dehydration	Severe dehydration
Look at			
• General condition	Well alert	Restless, irritable	Lethargic, unconscious
• Eyes	Normal	Sunken	Sunken
• Tears	Present	Absent	Absent
• Mouth and tongue	Moist	Dry	Dry
• Thirst	Drinks normally, not thirsty	Drinks eagerly, thirsty	Drinks poorly/ unable to drink
Feel			
• Skin pinch	Goes back quickly	Goes back slowly	Goes back very slowly
Decide			
	The patient has no signs of dehydration	Two or more signs denote some dehydration	Two or more signs denote severe dehydration
Treat	Use treatment Plan A	Use treatment Plan B	Use treatment Plan C urgently

**Fig. 29.2: Severe diarrheal dehydration.** Note the classical features.**Table 29.6: Dehydration scoring system**

Score 1	Score 2
<ul style="list-style-type: none"> • Irritability, drowsiness, or lethargy • Sunken anterior fontanel and/or eyes • Dry mucus membrane and/or skin • Loss of skin turgor • Abdominal distention • Tachycardia • Oliguria 	<ul style="list-style-type: none"> • Shock/coma • Acidosis • Anuria • Moribund state

Table 29.7: Composition of important intravenous solutions (mEq/L)

Solution	Na	K	Mg	Cl	HCO ₃
Isotonic saline (0.9% NaCl)	154	–	–	154	–
Ringer lactate	130	4	–	109	28
Half-strength Darrow's solution	61	18	3	52	27
Sodium bicarbonate (NaHCO ₃ 7.5%)	892	–	–	–	892
Sodium lactate (N/6)	167	–	–	–	167

If anuria persists despite rapid flushing in of the intravenous (IV) fluids, a bolus dose of frusemide may be administered. If the child passes urine, the IV drip is continued. Else, the child is treated as for acute renal failure (ARF)/injury, reducing the fluid intake considerably.

- **Continuation therapy:** For rest of the 24 hours, remaining four-fifth fluid is administered slowly. Here, half-strength Darrow's solution which is relatively rich in potassium is ideal. The aforesaid

plan of fluid therapy works well in a vast majority of the cases. It takes care of potassium deficiency as well as acidosis. Complications such as metabolic acidosis, paralytic ileus or hypocalcemic tetany are rare with this regimen.

Maintenance of fluids and electrolytes should continue over the second 24 hours even if diarrhea has stopped in the very first 24 hours. In severe acidosis (CO₂ <8 mEq/L),

it is advisable to give additional alkali (which should be infused) in amounts as per the following formula:

$$\text{mL of NaHCO}_3 (7.5\%) = \text{bicarbonate deficit (mEq/L)} \times \text{body weight (kg)} \times 0.5.$$

In situations where it is difficult to determine the base deficit, sodium bicarbonate may be given in the dose of 2–3 mL/kg. It is advisable to review the child after 2 hours to find if further correction is needed.

In case of **severe hypokalemia**, additional potassium in the dose of 1–3 mEq/kg may be added to the drip. Contrary to earlier recommendation, insistence on passing urine freely before potassium is administered is not necessary. If possible, an ECG should be done. In the event of occurrence of hyperkalemia, exchange resins, or digoxin are of value. IV NaCl and Ca are also helpful. **For hyponatremia**, full-strength electrolyte solutions and even 3% NaCl may be used. **Significant hypernatremia** requires solutions with sodium content of around 30 mEq/L. Highly diluted solutions may cause convulsions and other neurologic manifestations. Rarely, very serious cases of hypernatremia may need peritoneal dialysis as is done in the case of ARF. Finally, it needs to be remembered that plain solutions, like 5% glucose, should never be used for IV dehydration correction.

World Health Organization (WHO) Guidelines on the Management of Diarrheal Dehydration

Plan A for—No dehydration

- **Objective:** Prevention of dehydration. It is carried at home and consists of:
 - ORS administration, in amounts exceeding normal requirements:
 - <6 months 50 mL (1/4th glass)
 - 7 months to 2 years 50–100 mL (1/4–1/2 glass)
 - 2–5 years 100–200 mL (1/2–1 glass)
 - Later As much as the child accepts
 - Continuing normal feeding
 - Asking the caretaker to bring back the child after 2 days (even earlier in the presence of danger signals such as fever, repeated vomiting, dehydration, blood in stools).

Plan B for—Some Dehydration

- **Objective:** Correction of dehydration and prevention of malnutrition.
 - Correction of dehydration is carried out by administering ORS, 75 mL (50–100 mL)/kg over a period of 4 hours
 - Continuing breastfeeding/other feedings
 - Reassessment after 4 hours:
 - If adequately rehydrated, deal as in Plan A
 - If poor response to ORS, treat as in Plan C.

Plan C for—Severe Dehydration

- **Objective:** Quick correction of severe dehydration with IV fluids (preferably Ringer's lactate) in a hospital/facility.

- <1 year 30 mL/kg within first hour followed by 70 mL/kg over next 5 hours
- >1 year 30 mL/kg within 1/2 hour followed by 70 mL/kg over next 2 ½ hours
- Assess every 1–2 hours.
 - If no improvement, give IV fluid more rapidly
 - If improvement, complement with ORS as soon as the infant starts accepting it
 - After 6 hours in infants and 3 hours in older children, opt for the suitable plan A, B or C, depending on the assessed hydration status.

Antibiotics

Bacterial or parasitic organisms are not isolated from a large majority of pediatric patients suffering from acute diarrheal disease. Routine use of antibiotics is, therefore, generally not favored by the experts. However, antibiotic cover may be indicated in the following situations:

- Bloody diarrhea (bacillary dysentery)
- Cholera
- Amebiasis
- Giardiasis
- Malnutrition.

Pharmacotherapy for Symptomatic Control

In the past, nonspecific antidiarrheal agents, like codeine, morphia, tincture opium, charcoal, chalk, anticholinergic drugs, products of hydroscopic bulk (psyllium seed or Plantago ovatum), kaolin, bismuth, pectin, diphenoxylate hydrochloride and loperamide hydrochloride have been used. These drugs are either not quite effective or their use is accompanied by unpleasant/untoward side-effects. These are no longer recommended.

The role of prostaglandin inhibitors and antisecretory agents, such as aspirin, though theoretically significant, needs detailed evaluation in the therapy. Racecadotril, an antisecretory drug, claims to reduce stool output and duration of diarrhea. However, its efficacy remains to be convincingly proved. Its routine use in acute diarrhea is not yet recommended.

Nutrition (Diet)

Prolonged starvation damages rather than helps and should be discouraged. Even hypocaloric oral therapy during an episode of diarrhea and vomiting may lead to severe malnutrition. Lack of attention to nutrition during diarrhea appears to be the largest contributing factor to overwhelming problem of malnutrition in the Indian subcontinent.

Banana, apple pulp, yoghurt, curd, potatoes, rice, wheat, etc. should be given as soon as possible. Foods rich in fats or sugar, including juices and soft drinks, should be avoided.

Current recommendations on nutritional management of acute diarrhea are as follows:

- Since most nutrients are well-absorbed during diarrhea and since diarrhea predisposes to malnutrition, it is safe and desirable to continue breastfeeding as also other feedings during a diarrheal episode. That rest to gut promotes early recovery is no longer held true. It has no physiologic basis at all.

- 556** ■ Optimally, energy-dense foods with minimal bulk, given in small quantities every 2–3 hours, promote better nutrition.
- Since staple foods do not provide optimal calories per unit weight, these are best enriched with richer sources of energy, like fats and oils, e.g. *khichri* with oil, rice with milk or curd, mashed banana with milk or curd, mashed potato with oil, etc.
 - Foods with high fiber content (coarse fruits and vegetables) as also soft drinks and juices with very high sugar content may be avoided during an acute diarrheal episode.
 - In artificially-fed infants, milk should preferably be given undiluted during all phases of acute diarrhea. If the infant is over 4 months, milk cereal mixture (say dalia-sago, rice-milk) is strongly recommended.
 - Transient lactose intolerance, which is frequent in acute diarrheal disease, does not warrant lactose-free milk unless it persists beyond 8–10 days and is accompanied by progressive weight loss.
 - During convalescence from acute diarrhea, dietary intake should be enhanced by at least 25% of normal to make up for the losses during illness and to promote rapid weight gain until the child attains normal nutritional status.

Finally, it is most appropriate to re-emphasize the WHO/United Nations Children's Fund (UNICEF) slogan that the full package for diarrhea therapy in a vast majority of children is ORS and continued feeding.

Ancillary Measures

These include control of vomiting by sips of ORS, a mild antiemetic or stomach wash, and treatment of any other accompanying problem.

- **Zinc**, 10–20 mg/day (O), in every child with diarrhea, for 2 weeks is strongly recommended by the Indian Academy of Pediatrics (IAP). It helps in cutting down severity and duration of diarrhea. Furthermore, it reduces the risk of developing persistent diarrhea.
- **Probiotics**, may be helpful to restore the normal intestinal flora (lactobacilli) which are likely to be destroyed by the disease or by antibiotic therapy. However, at present, routine use of probiotics is not recommended by the IAP.
- **Vitamin A supplements may**, assist healing of the damaged intestinal epithelium.
- If IV drip is to be prolonged, vitamins should be added to the infusion.
- **Abdominal distention**, if mild and with normal bowel sounds, warrants no intervention. Paralytic ileus, manifested by gross abdominal distention and poor or absent bowel sounds, is an indication for temporary withdrawal of oral feeds, intermittent nasogastric

suction and administration of potassium chloride with a parenteral fluid. The existence of septicemia or enterocolitis should be seriously considered and treated energetically.

- Seizures during acute diarrhea may result from several factors, namely fever, hypo or hypernatremia, hypoglycemia, hypocalcemia (consequent upon administration of bicarbonate for correction of acidosis), meningitis, encephalitis, cavernous sinus thrombosis, etc. After symptomatic control of seizures with IV diazepam/lorazepam (or another suitable anticonvulsant) has been attained, attention should be paid to treat the etiologic basis of seizures.

Prognosis

- **Age:** Mortality is higher in newborns and infants than in older children.
- **Nutritional status:** Diarrhea in malnourished children carries poor prognosis*. Even mild-to-moderate diarrhea in such subjects may cause almost irreversible metabolic alterations, causing death. In one investigation, while the mortality in well-nourished patients was 4.3%, it was 22% in those suffering from marasmus.
- **Causative organism and severity of illness:** *E. coli* resistant to most available antibiotics and *Shigella* cause very severe illness.
- **Associated illness/complications:** Presence of profound dehydration, electrolyte imbalance or bronchopneumonia definitely has adverse effect on the outcome.
- **Management:** Promptness and adequacy of treatment also have great bearing on the ultimate outcome.

Prevention

- **Improvement in the nutritional status of the children:** Malnutrition predisposes to diarrhea which further aggravates the state of poor nutrition
- **Improvement in community's water supply, sanitation and hygiene:** Mothers must ensure proper handwashing before serving, preparing or eating food, using clean (potable), preferably boiled or filtered, drinking water, protecting food from contamination by flies, cockroaches and dirt, washing fruits and vegetables before use, and proper disposal of excreta (Fig. 29.3).
- **Breast (biological) feeding should be encouraged:** Those who are bound to stick to artificial feeding should learn the hygienic preparation of the formula and care of bottle, teats, etc.
- Mothers must be taught when to consult the doctor in case of diarrhea.
- Standardized simple method of administering IV fluids should be available not only in the cities but in rural areas as well.

* Children with significant protein energy malnutrition (PEM) often suffer from hypotonic dehydration. This observation is in sharp contrast with the picture seen in other children in whom dehydration is usually of isotonic type. Malnourished children, should, therefore, receive:

- Either isotonic or even hypertonic solution.
- Additional potassium.
- Additional sodium bicarbonate or sodium lactate to combat severe acidosis.
- Relatively less amount of fluids.

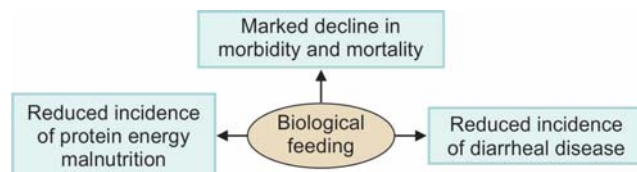


Fig. 29.3: Major gains of biological feeding.

- Easy availability of take-home ORS sachets.
- **Rotavirus vaccine:** Two doses of RV-1 is given in 10 and 14 weeks' schedule. RV-5 is given in three doses in 6, 10 and 14 weeks' schedule.

Complications/Sequelae

- Dehydration and dyselectrolytemia with its widespread complications, including acute kidney injury, paralytic ileus, thromboembolism, seizures, etc
- Superadded infections including thrombophlebitis at the site of catheter/cutdown
- Overhydration and CCF
- Malnutrition
- Hypoglycemia
- Syndrome of inappropriate secretion of antidiuretic hormone (ADH)
- Carbohydrate intolerance and persistent diarrhea
- Subdural collection of fluid/blood that may possibly cause mental retardation in later life
- Consumptive coagulopathy
- Toxic megacolon.

CHOLERA

This is a form of severe gastroenteritis characterized by sudden onset of profuse effortless watery diarrhea followed by vomiting and severe dehydration. The most severe form of cholera is termed as **cholera gravis**.

Etiology

The causative agent is labeled as *Vibrio cholerae* 01 or *V. cholerae* 0139 Group 1. The classical biotype is now by and large replaced by the E1 T or biotype mostly belonging to the serotype Ogawa.

In addition to the known 138 serotypes of *V. cholerae*, a new serotype (non-01) identical to the Indian serotype has been identified in Bangladesh. It behaves like *V. cholerae* 01 in causing a severe disease through production of a large quantity of cholera toxin.

Epidemiology

Though epidemics are now infrequent (the July–August 1988 outbreak in Delhi and other parts of the country was the most remarkable in the recent decades), cholera is currently endemic in Maharashtra, Tamil Nadu, Madhya Pradesh, Andhra Pradesh and Assam. These states account for 80% of the total incidence in India. Bengal is no longer considered as the home of cholera.

The disease is transmitted by the feco-oral route, the channels of transmission being contaminated water, contaminated foods or drinks, or direct person-to-person

contact. Poor environmental sanitation, thus, constitutes the lifeline for spread of cholera.

Clinical Features

Incubation period is 1–2 days with a variation of few hours, to 5 days. Clinical picture shows the following three stages:

1. **Stage I (stage of evacuation)** is characterized by profuse, effortless watery diarrhea with rice-water appearance (as many as 50 motions/day) followed by vomiting and rapidly developing dehydration.
2. **Stage II (stage of collapse)** is characterized by severe dehydration, eventually ending up in shock, which may prove fatal.
3. **Stage III (stage of recovery)** is characterized by signs of clinical improvement in subjects who have escaped death.

Diagnosis

In suspected cases needs to be confirmed by:

- Direct microscopy of samples of stool, vomitus, water or food. Under dark field illumination, organisms appear as several shooting stars in a dark sky
- Culture on peptone water tellurite (PWT) medium
- Biochemical tests.

Complications

These include acute renal shutdown, hypokalemic nephropathy, paralytic ileus, pulmonary edema and arrhythmias.

Management

Treatment consists in administering oral and/or IV rehydration therapy along with chemotherapy to cut short the duration of disease as also to reduce period of vibrio excretion. Drug of choice is tetracycline but, in view of its known adverse side-effects in children, the choice should be out of erythromycin, azithromycin, Furazolidone ciprofloxacin and cotrimoxazole. A 3-day course is sufficient. Whereas *V. cholerae* 0139 is resistant to cotrimoxazole, tetracycline-resistant strains of *V. cholerae* 01 have also occurred in many countries.

Attention must also be directed to sanitation measures such as water control, excreta disposal, food sanitation and disinfection. The innovative **cholera cot** developed by the Diarrheal Disease Center, Dhaka, Bangladesh, is of great utility. It is a portable cot with a hole in the middle, leading to a bucket underneath.

Prophylaxis

Chemoprophylaxis (same drugs as for treatment and for the same period) is recommended for household contacts or for a closed community with outbreak of cholera. **Oral cholera vaccine** is recommended in children > 1 year of age in two doses 2 weeks apart, and in persons residing in highly endemic areas or traveling in areas where risk of transmission is very high, like Kumbh Mela.

Box 29.3 Subdivisions of *Shigella*

- **Group A:** *Shigella shiga* or *dysenteriae* is the most important among the ten serotypes
- **Group B:** *Shigella flexneri* or *paradysenteriae* is the most important among the six serotypes
- **Group C:** *Shigella boydii*
- **Group D:** *Shigella sonnei*.

ACUTE BACILLARY DYSENTERY**(Bloody Diarrhea, Shigellosis)****Definition**

It is defined as the passage of loose stools containing mucus, pus and visible blood, and accompanied by fever, tenesmus and crampy abdominal pain.

Etiopathogenesis

The causative organism, *Shigella*, is subdivided into four groups (Box 29.3).

Invasive strains of *Shigella*, after penetrating the epithelial cells of the intestine, multiply in the submucosa and lamina propria. This leads to local inflammation and superficial ulcers which may bleed.

Epidemiology

Shigellosis occurs worldwide, usually towards the late summer. The disease spreads chiefly by oral-fecal route. The spread is boosted by the low level of personal hygiene, environmental sanitation level causing breeding of flies, and contamination of water, ice, milk and other foods. Both sporadic and epidemic forms occur.

Clinical Features

Incubation period is usually 1–3 days. Onset is sudden with fever, prostration, vomiting, bloody diarrhea, abdominal pain and tenesmus. Dehydration and electrolyte loss may cause shock. Headache, drowsiness and even coma, neck rigidity and convulsions may occur.

Differential Diagnosis

Table 29.8 lists the major differential diagnosis of bloody diarrhea in children.

Diagnosis

- Stool sample shows leukocytes (pus cell) and red blood cells.

- Blood counts reveal a marked leukocytosis with rise of polymorphonuclear cells in majority of the cases.
- Stool cultures for isolating the organism are essential for establishing the diagnosis.

Treatment**Specific**

Choice of antibiotic depends on the existing sensitivity of the organism in the particular community. In the wake of increasing resistance to ciprofloxacin, ampicillin, cotrimoxazole, nalidixic acid, etc. The following approach is most appropriate:

- **Children with bacillary dysentery who are stable:** Ciprofloxacin, cefixime or azithromycin
- **Children with bacillary dysentery who are very sick:** Ceftriaxone should be considered the current drug of choice.

General Measures

These include correction of dehydration and electrolyte imbalance and associated malnutrition, including hypoproteinemia and anemia. Antimotility drugs such as diphenoxylate and loperamide may decrease frequency of motions, but prolong excretion of *Shigella*, and are best avoided.

Prognosis

Institution of proper treatment well in time leads to a favorable prognosis in a large majority of the cases. Factors such as malnutrition and enclosed population (say, that of mental institution) contribute to increased morbidity and mortality.

Complications include anemia with hypoproteinemia, rectal prolapse, arthritis, Reiter's syndrome, vaginitis and hemolytic uremic syndrome. A chronic form of shigellosis may occur. In such a carrier state, a synthetic derivative of lactose (lactulose) may transiently reduce the excretion of the organisms.

Prevention

This is by control of carrier and active states and attention to personal, water and food hygiene and environmental standards. No vaccine is so far available against shigellosis.

ANTIBIOTIC-ASSOCIATED DIARRHEA**Definition**

Antibiotic-associated diarrhea (AAD) is defined as diarrhea that has no known cause other than antibiotic therapy given concurrently or, at the most, 4 weeks preceding it.

Table 29.8: Major differential diagnosis of bloody diarrhea

Group	Pathogens/Conditions
Invasive bacteria	<i>Shigella</i> , <i>coli</i> (enteroinvasive, enterohemorrhagic, <i>Campylobacter jejuni</i> , <i>Salmonella</i> (nontyphoidal)
Protozoa/helminths	<i>Escherichia histolytica</i> (both luminal and invasive), <i>Giardia lamblia</i> , <i>Hymenolepis nana</i> , <i>Strongyloides stercoralis</i> , hookworm
Miscellaneous/noninfectious	Intussusception, vitamin K deficiency, ulcerative colitis, Crohn's disease, blood dyscrasias (leukemia), purpura (ITP).

Abbreviations: ITP, idiopathic thrombocytopenic purpura; HSP, Henoch-Schönlein purpura.

Blood in stools is not mandatory. On the contrary, stools may be frequent, watery and voluminous with or without gross (visible) blood or mucus.

Etiopathogenesis

Any antibiotic is capable of causing diarrhea. However, the following are considered the high-risk antibiotics for AAD:

- Clindamycin
- Ampicillin
- Lincomycin
- Macrolides, especially azithromycin
- Cephalosporins.

Antibiotics are supposed to cause diarrhea through *C. difficile* which produces adverse effects on intestinal mucosa through its toxins. Toxin A acts on the intestinal mucosa to produce diarrhea. Toxin B, a cytotoxin, enhances vascular permeability in low doses, but in higher doses, it may prove lethal.

Additional mechanisms (other than toxin) of production of diarrhea by *C. difficile* are:

- Suppression of the normal gut flora.
- Production of enzyme, beta-lactamase, by resistant pathogens, thereby inactivating antibiotics and facilitating growth of *C. difficile*.

Clinical Features

- Manifestations range from mild self-limited diarrhea without pseudomembrane through explosive watery diarrhea with occasional blood to severe hemorrhagic colitis with classical picture of blood and mucus accompanied by toxemia in pseudomembranous colitis.
- Toxic patient may have fever, cramps, crampy abdominal pain, nausea and vomiting, dehydration with dyselektrolytemia, protein-losing enteropathy and hypoalbuminemia.
- Serious complications such as toxic megacolon, colonic perforation, peritonitis and shock may occur.

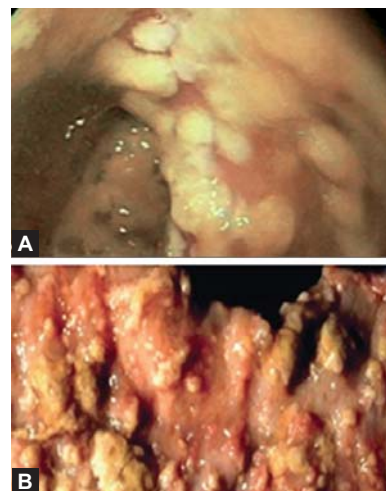
Diagnosis

A high index of suspicion is the key in detecting cases of antiepileptic drug (AED), including pseudomembranous colitis. Diagnosis needs detection of the organism, *C. difficile* (culture), as also the toxin A (enzyme-linked immunosorbent assay {ELISA} or latex agglutination assay) and toxin B (cytotoxicity to cultured fibroblasts).

Colonoscopy may be of value in visualizing the lesions in atypical cases:

- **Stage 1:** Normal appearance
- **Stage 2:** Mild edema and erythema
- **Stage 3:** Granular friable or hemorrhagic mucosa
- **Stage 4:** Pseudomembranous colitis.

Typically, pseudomembranous nodules or plaques occur in rectum, sigmoid and distal colon. In a proportion of cases these may be found only in cecum and transverse colon. The lesions appear as grayish-white exudates that are surrounded by edematous and erythematous inflammatory response (Figs 29.4A and B). These are poorly adherent to the underlying tissue.



Figs 29.4A and B: Pseudomembranous colitis. (A) Multiple yellow plaques throughout colonic mucosa; (B) Flat raised lesions that vary in size with intervening hyperemic mucosa.

Differential Diagnosis

Differential diagnosis is from:

- Diarrhea due to *Shigella*, *Salmonella*, *E. coli*, *Yersinia*, *Helicobacter*, *E. histolytica*, *G. lamblia*, *S. stercoralis*, *T. trichiura*, or *H. nana*
- Hemolytic uremic syndrome (HUS)
- Inflammatory bowel disease
- Neutropenic colitis
- Typhilitis
- Malabsorption states.

Treatment

Discontinuation of the suspected drug and rehydration therapy, if dehydration is present, results in remarkable improvement within 48 hours and complete resolution within 7–10 days in mild cases.

If response is unsatisfactory within 48–72 hours or in case of a severe illness (pseudomembranous colitis), the following drugs are recommended:

- Oral metronidazole, ornidazole or nitazoxanide
OR
- Oral vancomycin (20–40 mg/kg/day) yet more critical situations (toxic megacolon, adynamic ileus), a combination of the two drugs intravenously (IV) is recommended.

If the patient fails to respond to one, it may be substituted by the other. In yet more critical situations (toxic megacolon, adynamic ileus), the two drugs may well be administered IV and simultaneously. Supportive measures include use of probiotics for restoration of normal gut flora and inhibition of growth of *C. difficile*.

Prognosis

Recurrences may occur in a proportion of the cases. Oral cholestyramine, bacitracin, immune globulin, lactobacilli, Baker's yeast or instillation of fecal flora may work in such subjects.

Prevention lies in judicious use of antibiotics plus good food and personal hygiene, meticulous handwashing and proper environmental cleaning. A vaccine is around the corner. Algorithmic approach for antibiotic-associated diarrhea is shown in Figure 29.5.

ORAL REHYDRATION THERAPY

Oral rehydration means drinking a solution of clean water, sugar and mineral salts to replace the water and salts lost from the body during diarrhea, especially when accompanied by vomiting, the so-called *gastroenteritis*. Studies conducted all over the world, particularly in Bangladesh, India and Indonesia, have established the value of this revolutionary concept in counteracting dehydration which is known to be the main cause of death in acute diarrheal disease, a major public health problem.

ORS is now distributed internationally by the UNICEF in packets labeled ORS and also manufactured commercially by several pharmaceutical houses for sale on prescription.

Indications

ORS is beneficial in three stages of diarrheal disease, namely:

Table 29.9: Low osmolarity ORS vis a vis standard oral rehydration salts

Component	Standard ORS	Low osmolarity ORS
Contents		
Sodium chloride	3.5 g	2.6 g
Sodium bicarbonate (citrate)*	2.5 g (2.9 g)	2.9 g
Potassium chloride	1.5 g	1.5 g
Glucose	20.0 g	13.5 g
Osmolarity		
Sodium	90 mOsm	75 mOsm
Chloride	80 mOsm	65 mOsm
Citrate	10 mOsm	10 mOsm
Potassium	80 mOsm	20 mOsm
Glucose	111 mOsm	75 mOsm
Total osmolarity	311	245

* Replacement of sodium bicarbonate by trisodium citrate dihydrate (2.9 g) undoubtedly enhances the shelf-life of the ORS but also makes it more expensive. The ORS thus prepared provides 10 mmol/L of citrate in place of 30 mmol/L of bicarbonate (one mmol citrate = 3 mmol base).

Abbreviation: ORS, oral rehydration salts.

1. Prevention of dehydration if initiated right at the beginning of an episode of diarrhea.
2. Rehydration of the dehydrated child so that he does not enter the phase of severe dehydration in which IV fluids may become necessary
3. Maintenance of hydration after severely dehydrated patient has been rehydrated with IV administration.

Standard Formulation

The standard formulation, recommended by WHO until recently has an osmolarity of 311 mOsm/L (Table 29.9).

Low Osmolarity ORS

Recently, WHO has done well to introduce a low osmolarity ORS (Table 29.9) to cut down risk of hypernatremia which earlier restricted its wide usage in neonates and infants. This formulation provides a total osmolarity of 245 mOsm/L compared to the standard WHO formulation with 311 mOsm/L. It is supposed to lower stool output, shorten diarrheal duration and reduce vomiting. It may be given at all ages. IAP has pleaded for easy availability of yet lower osmolarity oral rehydration salts (224 mOsm/L) for infants <2 months.

ReSoMal (ORS in severely malnourished children)

Oral rehydration salts for severely malnourished children needs to be special in order to provide high potassium and low sodium. WHO recommends ReSoMal for this purpose. Though commercially available, it can be prepared by diluting standard WHO, ORS in 2 liters of water rather than one liter and adding 50 g sucrose (in place of 20 g)

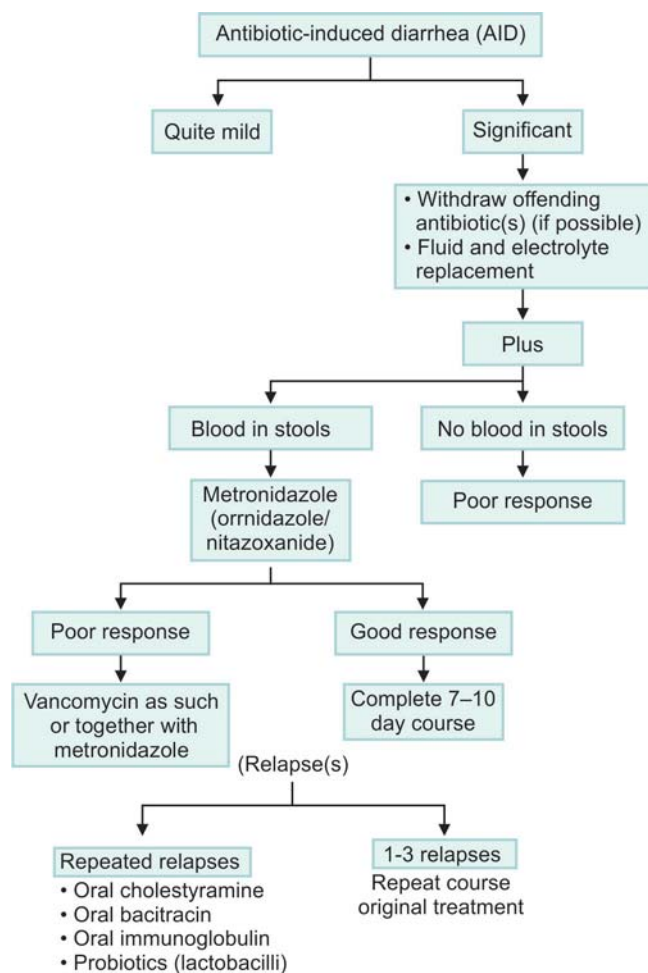


Fig. 29.5: Algorithmic approach for antibiotic-associated diarrhea.

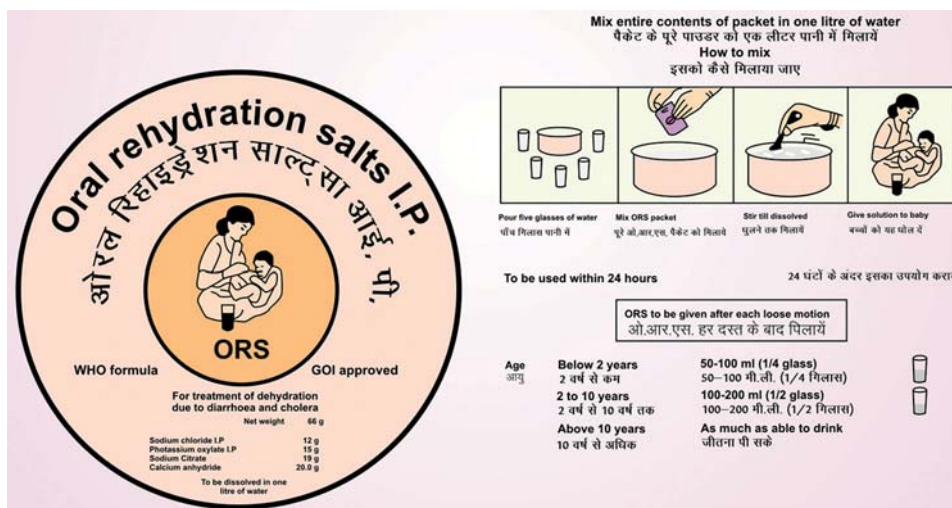


Fig. 29.6: Oral rehydration salts sachets must bear logo and instructions for use as shown here.

and 40 mL of mineral mix which, among other minerals, provides high content of potassium chloride. This solution is administered in a dose of 70–100 mL/kg over 12 hours (Fig. 29.6).

Home-made Preparations of ORS

Several studies with home-made preparations as also our own experience with them have given gratifying results.

How to make ORS at home? The easiest approach is to mix one three-finger-pinch (1/2 teaspoonful) of common salt and two four-finger-scoops (5 teaspoonful) of sugar in one liter of tap or boiled water. Addition of lemon or orange juice, coconut water, mashed tomato, papaya or banana to this solution brings it close to the recommended WHO formulation. Even if none of these can be procured, it does not matter. It has been demonstrated that potassium and bicarbonate may not be essential in the early stages of dehydration. Also, there is nothing wrong in replacing sugar or glucose with molasses (gur) (Fig. 29.7).

Substituting a polymeric form of glucose (starch) of the WHO ORS for the single molecule form results in solution that may perform better than the standard ORS. Hence the designation **super ORS**. This has led to the concept of cereal-based oral rehydration therapy (ORT) (Box 29.4), the best studied so far being RWES. RWES consists of decanted solution after cooking rice. Salt is added to it. This may also be prepared by dissolving 2-finger scoops of rice powder (boiled rice) in water and boiling for 3 minutes. To it are added a pinch or two of salt and 1/4th medium size lemon juice.

Alternative home-made electrolyte solutions include:

- Dal and water solution, carrot juice, tender coconut water, Bengal gram kanji, weak tea, fruit juices, banana
- Honey-based—one teaspoonful of honey + pinch of salt + one glass water
- Arrowroot kanji + salt
- Butter milk + salt + with or without sugar and lemon.

Since diarrhea and vitamin A deficiency are beginning to be considered as risk factors for each other, fortification of ORS

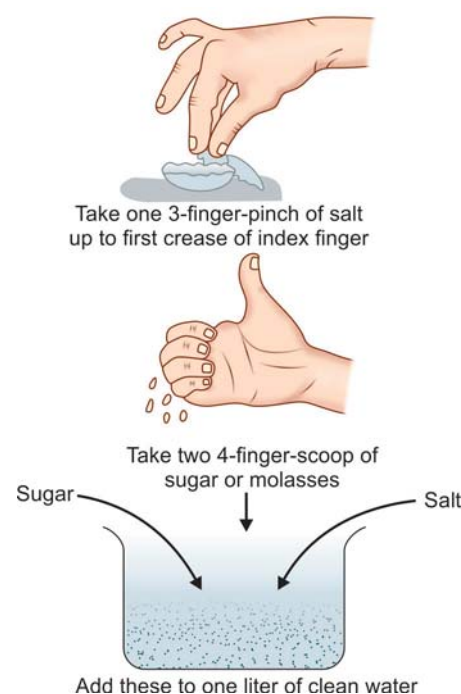


Fig. 29.7: Preparing oral rehydration solution at home.

Box 29.4

Advantages of cereal-based oral rehydration solution

- More palatable
- Provides more energy
- Reduces stool volume; hence less diarrheal fluid losses
- Controls/lessens vomiting during treatment
- Shortens duration of diarrhea
- Ingredients (cereals, starchy vegetables) easily available in households
- RWES is more palatable. Babies not responding to the standard ORS may respond to it.

with vitamin A, or, at least, linkage of distribution of vitamin A and ORS sachets has been advocated. This may prove an effective strategy reducing the morbidity accompanying diarrheal dehydration and vitamin A deficiency.

562 Administration

Ideally, each motion should be followed by replacement of as much fluids. Illiterate mothers, however, may not be able to judge the amount of fluid loss. In such cases, let them give the child as much ORS as he desires. But, it is unwise to push the fluids if the child does not accept these or if vomiting is persisting. Giving ORS in sips often helps to tide over this difficult situation.

Limitations

- A common criticism of standard ORT is that it may cause hyponatremia, resulting in convulsions, cerebral hemorrhage and often death. The availability of low osmolality ORS has overcome this criticism.
- Glucose malabsorption may occur in a small proportion of cases, thereby worsening the diarrhea and dehydration.
- ORT may not be the answer in a proportion of the cases with severe dehydration leading to shock, anuria and acidosis. It may also flop in severe vomiting and high rate of stool loss.

PERSISTENT DIARRHEA

Definition

The term, **persistent diarrhea**, is employed when an episode of acute diarrhea/gastroenteritis (invariably infective in etiology) continues beyond 2 weeks period. Invariably, it starts off as an acute infective episode that stretches beyond 2 weeks in at-risk infants and children. More than dehydration, these patients suffer from deteriorating nutritional status.

According to conservative estimates, some 7–25% children in preschool age group who suffer from acute gastroenteritis may end up with persistent diarrhea in the resource-limited countries such as ours. Peak incidence is around 1 year of age. It contributes considerably to malnutrition. In subjects under 1 year, mortality is particularly high. When persistent diarrhea develops before the age of 3 months, it is often termed as **intractable diarrhea of infancy**.

Etiology

Persistent diarrhea is as yet an entity of obscure etiology. Identifiable risk factors are listed in Box 29.5.

Clinical Features

Three clinical types are recognized:

1. Subjects with several motions/day, but without any adverse fallout on nutritional status and growth and development
2. Subjects with several motions (without dehydration), and malnutrition and growth retardation
3. Subjects with several motions and dehydration that is difficult to control by ORS.

In the subjects belonging to the second and third categories, manifestations include progressive weight loss, malnutrition, anorexia, malabsorption and secondary infections.

Box 29.5

Risk factors for persistent diarrhea

- Age between 6 months and 1 year; after 2 years of age, risk of persistent diarrhea is reduced
- LBW and malnutrition; vitamin A deficiency
- Diarrheal episode with blood and mucus such as caused by enteropathogenic or aggregative adherent *Escherichia coli*, *Shigella*, *Salmonella*, *Campylobacter jejuni*, and *rotavirus*, especially in infants <3 months of age
- Excessive fluid intake, especially carbonated drinks and fruit juices
- Artificial feeding
- Indiscriminate use of ORS, especially with high sugar content
- Lactose intolerance
- Systemic infections like septicemia
 - Irrational antibiotic use, causing bacterial/fungal overgrowth and persistent diarrhea
- Milk protein allergy
- A preceding diarrheal episode in the recent past may make the child vulnerable to yet another episode that becomes persistent. The factors that contribute to persistent diarrhea in such a situation include deterioration in nutritional status, damage to small intestinal mucosa, contamination of animal milk and osmotic diarrhea
- Intestinal parasitosis.

Abbreviations: ORS, oral rehydration salts; LBW, low birth weight.

Diagnosis

It is by and large clinical with support from screening laboratory tests. The latter must include meticulous stool microscopy, on at least 6 successive days for ova and cysts. A stool culture is warranted. An acidic diarrheal stool is an indication for demonstration of reducing substances in stools, a highly fatty stool for fat balance studies, persistent diarrhea with recurrent chest infection for sweat chloride and persistent diarrhea with skin lesions for serum zinc level.

Treatment

Diet

Dietary manipulation along with rehydration therapy is the backbone of management of persistent diarrhea. Breastfeeding must continue. Though diarrhea may continue despite breastfeeding, infant's nutrition remains maintained and he may even gain some weight. Box 29.6 lists highlights of the three recommended diets in management of persistent diarrhea.

1. **Diet A:** In case persistent diarrhea is mild, the infant on artificial feed (should be given milk mixed with a cereal (Table 29.10) or curd rather than milk as such.
2. **Diet B:** In case persistent diarrhea is severe, as manifested by dehydration, high purge rate (over 7 mg/kg/hour) or very frequent large and watery stools, total milk elimination in an artificially fed infant is needed. Table 29.11 lists the composition of an egg-based milk-free diet for persistent diarrhea. Breastfeeding, reduced intake of other milk, or its total withdrawal should be supplemented with enriched gruels like *khichri* with oil, lentil with oil, mashed potato with oil, curd mixed with mashed potatoes or banana or rice with added sugar.

Box 29.6**Three recommended diets in persistent diarrhea****Diet A (low lactose diet)**

- Reduced (not totally eliminated) lactose (milk), e.g. milk-rice gruel, rice-curd, *dalia*; even milk-banana.
- **Indication:** Initial diet in persistent diarrhea.

Diet B (lactose, i.e. milk-free with reduced starch diet)

- Cereals + glucose for carbohydrates; egg, chicken or commercial protein hydrolysate
- No milk at all.
- **Indication:** Lactose intolerance/malabsorption.

Diet C (monosaccharide-based)

- Only glucose + egg white/chicken, oil
- Total elimination of disaccharides, i.e. no milk, no cereals
- **Indication:** Disaccharide intolerance/malabsorption.

Table 29.10: Composition of an initial milk-rice diet (diet A) for persistent diarrhea

Ingredient	Amount (g)
Puffed rice*	12.5
Milk	40.0
Sugar	2.25
Oil	2.0
Water	100.0 mL
Egg density	96 kcal/100 g
Protein	10.0%
Carbohydrate	55.87%
Lactose	1.73%
Fat	33.9%
Amino acid score	1.0%

* Puffed rice is ground and appropriate quantities are mixed with sugar and oil. Boiled water is then added to make a thick gruel. This feed has a shelf life of around 3 hours.

Table 29.11: Composition of an egg-based milk-free diet for persistent diarrhea

Ingredient	Amount (g)
Puffed rice	13.5
Egg*	11.0
Sugar/glucose	3.5
Oil	3.5
Water	100.0 mL
Egg density	92.2 kcal/100 g
Protein	9.5%
Carbohydrate	56.9%
Fat	33.29%
Amino acid score	1.0%

* Egg white is added to the mixture of weighed rice, sugar and oil. Boiled water is added to make a thick gruel weighing 100 g.

3. **Diet C:** In cases of severe persistent diarrhea that fails to respond to the dietary management outlined above, intolerance to disaccharides (other than lactose as well) becomes quite likely. Mono or oligosaccharide carbohydrates diet is well tolerated by these children.

Table 29.12: Chicken-based diet with glucose (diet C) for severe persistent diarrhea with likelihood of lactose and other disaccharide intolerance

Ingredients	Amount/liter	kcal (%)	Protein (g%)
Chicken	100 g	110	26
Glucose	20–40 g	160	–
Coconut oil	40–50 g	450	–
KCl (15%)	7.5 mL	–	–
NaHCO ₃ (7.5%)	20–30 mL	–	–
Total	1000 mL	720	26

Notes:

- It is prepared by grinding the precooked boneless chicken stuff in a mixie. Glucose, oil and some water are added to it and the feed is brought to a boil. Additional water is added to make a final volume of 1 liter. Finally, KCl and NaHCO₃ are added. To safeguard against spoilage, it is stored in a refrigerator
- Glucose is initially added in 2% concentration and then built upto 4% by increasing 1% every alternate day. To reduce osmolar load, a mixture of glucose and sugar may be employed
- Any vegetable oil may be employed in place of coconut oil.

All disaccharides need to be eliminate. Table 29.12 gives details of a chicken-based diet for such a persistent diarrhea.

Vitamins and Micronutrients

It is advisable to provide twice the maintenance requirements of vitamins, and trace elements like iron, and folate for a minimum of 2–4 weeks. Iron is best started after diarrhea has controlled. Zinc, 10–20 mg daily for 2 weeks, should be given to all infants and children with persistent diarrhea on dietary manipulation.

Vitamin A in a single oral dose (<6 months 50,000 IU, 6–12 months 100,000 IU and 1–3 years 2000,000 IU) should also be given.

Probiotics

Probiotics may be helpful in restoring the normal gut flora. As yet, there is insufficient evidence favoring their routine use in persistent diarrhea.

Antimicrobial Therapy

It is indicated in the presence of identifiable enteric pathogens such as *Shigella* or *E. coli*, when persistent diarrhea is bloody but culture facilities are not available, and when there is evidence of persistent diarrhea being secondary to a systemic infection like septicemia. In the so-called **bacterial overgrowth syndrome**, a combination of oral gentamicin (50 mg/kg/day 4 hourly for 3 days) and oral cholestyramine (1 g 6 hourly for 5 days) may prove useful. Antimotility drugs, kaolin and pectin are best left out.

Wormicidal

Metronidazole is recommended only for amebiasis, giardiasis, or anaerobic infections. Finally, parenteral nutrition (partial or total) may be indicated in very advanced cases when small bowel mucosa is extensively denuded, causing intolerance to even small amounts

564 of gruel (which moves out in stools) with significant weight loss. An algorithmic approach to management of persistent diarrhea is given in Figure 29.8.

Response to Therapy

Criteria for good response include:

- Reduction in frequency of diarrheal stools
- Improvement in appetite
- Improvement in dietary intake
- Weight gain.

Diet During Convalescence

During convalescence, most cases need relatively higher intakes for the catch-up growth.

Prevention

Promotion of breastfeeding and safe weaning practices together with prompt treatment of acute diarrhea with ORS or IV fluid therapy and attention to child's overall nutrition, during and after the diarrheal episode, should go a long way in safeguarding against development of

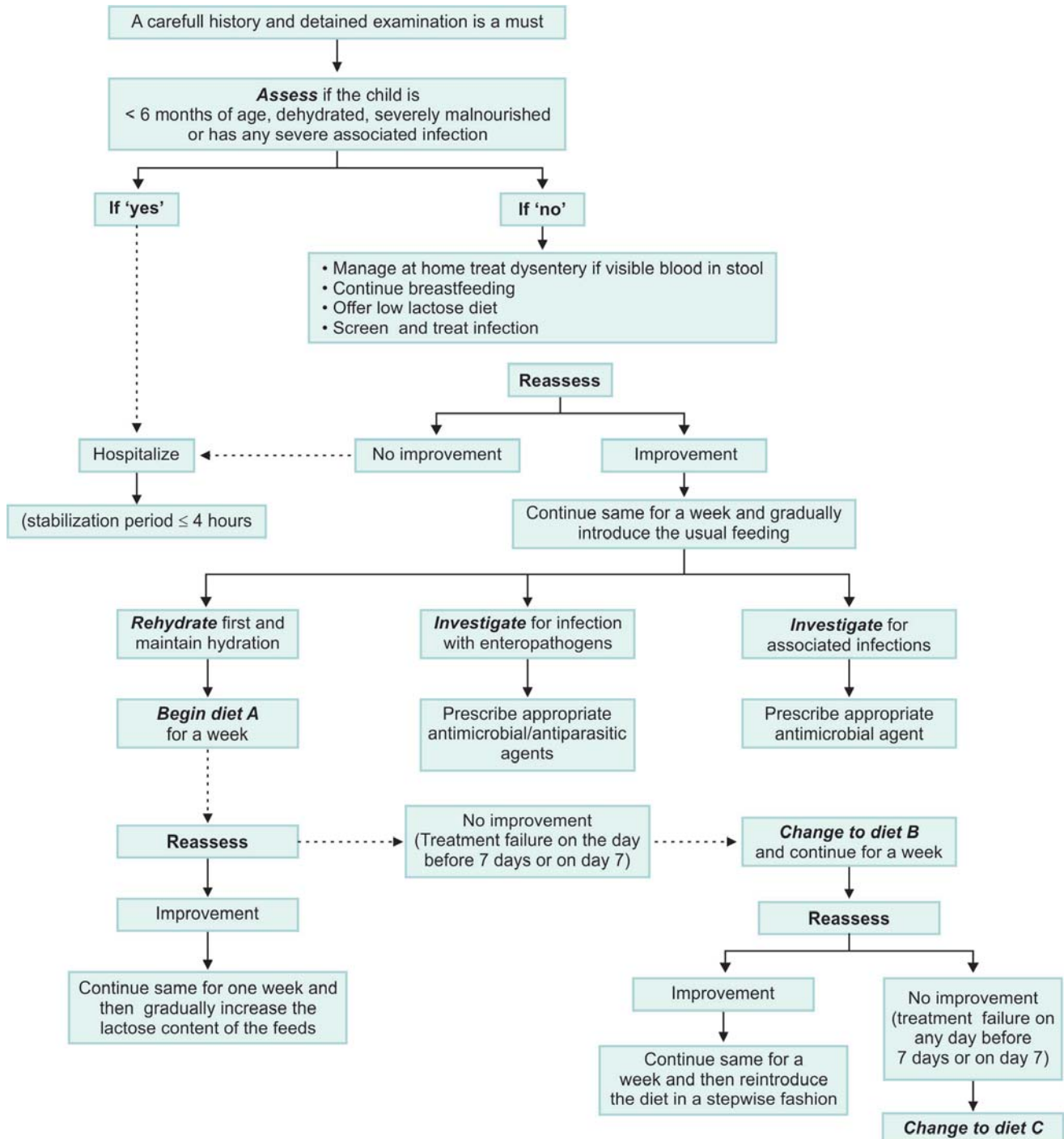


Fig. 29.8: Management algorithm for persistent diarrhea.

persistent diarrhea. Starvation therapy and exclusion of lactose from diet for mild transient lactose intolerance must be avoided, so should the indiscriminate use of ORS and antimicrobial therapy.

Prognosis

Most children with persistent diarrhea recover following stepped up dietary manipulation. Survivors are usually left with moderate to gross malnutrition. Inadequately treated or untreated persistent diarrhea causes high morbidity and mortality, particularly in infants. Determinants of poor outcome include:

- Systemic infections
- Severe lactose and/or monosaccharide intolerance.

CHRONIC DIARRHEA

Definition

Chronic diarrhea is defined as diarrhea of at least 2 weeks duration or 3 attacks of diarrhea during the last 3 months, usually due to obvious malabsorption or an organic or other cause without obvious malabsorption.

Though cutoff point for both persistent and chronic diarrhea remains 2 weeks, unlike persistent diarrhea, significant malabsorption is a prominent feature of chronic diarrhea. It is a common pediatric problem in tropical countries and is responsible for considerable ill-health and morbidity.

Evaluation Protocol

Roughly diagnostic evaluation of the child with chronic diarrhea should be step-by-step (Box 29.7) rather than by a large number of investigations at a time. The individual

Box 29.7

Four phases of evaluation of the child with chronic diarrhea/malabsorption

- **Phase I:** History and physical examination with special reference to onset of diarrhea and its relationship with various factors (excessive carbonated drinks/fruit juices, supplementary milk feeds, cereals), specific amount of fluids ingested/day, nutritional status, etc.
 - Meticulous stool examination (ova and cysts, pH, reducing substances, fat globules)
 - Stool culture
 - Stool for *C. difficile* toxin
 - Blood studies (CBC, ESR, electrolytes, BUN, creatinine).
- **Phase II:** Fat balance studies for daily stool fat or steatocrit
 - D-xylose test
 - Sweat chloride test
 - Stool osmolality and electrolytes, phenolphthalein, magnesium sulfate, phosphate
 - Breath H_2 tests.
- **Phase III:** Barium meal/enema to exclude anatomic defects small intestinal biopsy/colonic biopsy by endoscopic studies
 - Sigmoidoscopy/colonoscopy.
- **Phase IV:** Hormonal studies
 - Neurotransmittal studies (vasoactive intestinal polypeptide, gastrin, secretin, 5-hydroxyindoleacetic assays).

Abbreviations: CBC, complete blood count; ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen.

merits of each case and the proper application of knowledge and experience of the attending pediatrician contribute to deciding the necessary investigations.

Pathophysiologic Mechanisms

Osmotic diarrhea results from presence of malabsorption of water-soluble nutrients (lactose intolerance) and excessive intake of carbonated fluids or nonabsorbable solutes (sorbitol, lactulose, magnesium hydroxide) which cause an osmotic load in the colon. It shows good response to simple fasting.

Secretory diarrhea results from activation of intracellular mediators like cyclic adenosine monophosphate (cholera, heat-labile *E.coli*, *Shigella*, *Salmonella*, *C. jejuni*, *P. aeruginosa*, hormones like vasoactive intestinal peptide, gastrin, secretin, anion surfactants like bile acids and ricinoleic acid), cyclic guanosine monophosphate (heat stable *E.coli*, *Y.enterocolitica* and intracellular calcium (*C. difficile*, acetylcholine, serotonin, bradykinin).

Mutation defects in apical membrane (ion) transport proteins such as in chloride-bicarbonate exchange and sodium-bile acid transporter result in secretory diarrhea and FTT at birth.

Reduction in anatomic surface area in such conditions as short bowel syndrome following surgical resection in necrotizing enterocolitis, volvulitis or atresia. Alteration in intestinal motility in conditions such as malnutrition, diabetes mellitus, intestinal pseudo-obstruction syndromes and scleroderma. Here, diarrhea is of secretory type.

Etiologic Considerations

A large number of conditions, involving intraluminal factors, mucosal factors, or both, can cause chronic diarrhea (Box 29.8). Nevertheless, the scene is dominated by a few conditions.

- Is the child consuming excessive amounts of carbonated drinks or fruit juices (over 150 mL/kg/24 hours) and yet has normal growth and height parameters (nonspecific chronic diarrhea)? The problem usually resolves following reduction in fluids (under 90 mL/kg/24 hours).
 - Is the child having excessive intake of nonabsorbable nutrients such as sorbitol, $Mg(OH)_2$ or lactulose? A corrective action often controls the chronic diarrhea.
- As a result of extensive studies in North India, it has become exceedingly clear that etiology of chronic diarrhea in tropical children is much different from what is described in the textbooks from the western countries. Box 29.9 gives the relative incidence of important etiologic factors. Note that the common causes occupying the top positions.

Chronic Diarrhea/Malabsorption: A Practical Approach

The following approach is suggested for diagnosis and management of a child with chronic diarrhea and/or malabsorption in our set-up.

Box 29.8 Etiology of chronic diarrhea**Intestinal mucosal causes**• **Altered integrity:**

- **Infections/infestations:** Viral, bacterial, fungal, parasitic
- Cow's milk protein allergy/intolerance
- Soy protein allergy/intolerance
- Inflammatory bowel disease.

• **Altered immune function:**

- HIV/AIDS
- Autoimmune enteropathy

• **Altered function:**

- Abetalipoproteinemia
- Acrodermatitis enteropathica
- Tropical sprue
- Selective folate deficiency
- Defects in Cl^- , HCO_3^- , Na^+/H^+ .

• **Altered digestive function:**

- CF

• **Altered surface area:**

- Celiac disease
- Malnutrition
- Iron deficiency anemia
- Endemic tropical sprue
- Hookworm infestation.

• **Altered secretory function:**

- Enterotoxin—producing bacteria
- Vasoactive peptides—secreting tumors.

• **Altered anatomical structures:**

- Congenital megacolon
- Partial small bowel obstruction.

• **Altered motility:**

- Malnutrition
- Diabetes mellitus
- Intestinal pseudoobstruction
- Scleroderma.

Intestinal intraluminal causes

- Excessive intake of carbonated drinks
- Excessive intake of sorbitol, lactulose, magnesium salts
- Carbohydrate malabsorption
- Congenital monosaccharide malabsorption.

Pancreatic causes

- CF
- Chronic pancreatitis.

Bile-related disorders

- Chronic cholestasis
- Bacterial overgrowth
- Prolonged use of bile acid sequestrants
- Terminal ileum resection.

Miscellaneous

- Factitious diarrhea
- Toddler's diarrhea
- Chronic nonspecific diarrhea.

Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; CF, cystic fibrosis.

- A good history—the importance of a carefully taken history cannot be overemphasized. Most valuable pointers and clues are likely to be obtained from answers to the following questions:
 - Did the symptoms appear early in infancy (CF) or after the first six months of life (CD)?
 - Was there any relationship between onset of symptoms and introduction of supplementary milk feeds (lactose intolerance) or cereals (CD)?

Box 29.9 Causes of chronic diarrhea in Indian children

- PEM
- Iron deficiency anemia
- Excessive consumption of fluids (carbonated, fruit juices)
- Intestinal parasites (*Giardia lamblia*, hookworm, roundworm, *Entamoeba histolytica*, *Strongyloides stercoralis*, *Trichuris trichuria*, tapeworms)
- Intestinal infection (enteropathogens, *M.tuberculosis*)
- Celiac disease
- CF
- Endemic tropical sprue
- Carbohydrate intolerance
- Irritable colon syndrome
- Ulcerative colitis
- Miscellaneous (regional ileitis, anatomic defects, protein-losing enteropathy, etc.).

Abbreviations: CF, cystic fibrosis; PEM, protein energy malnutrition.

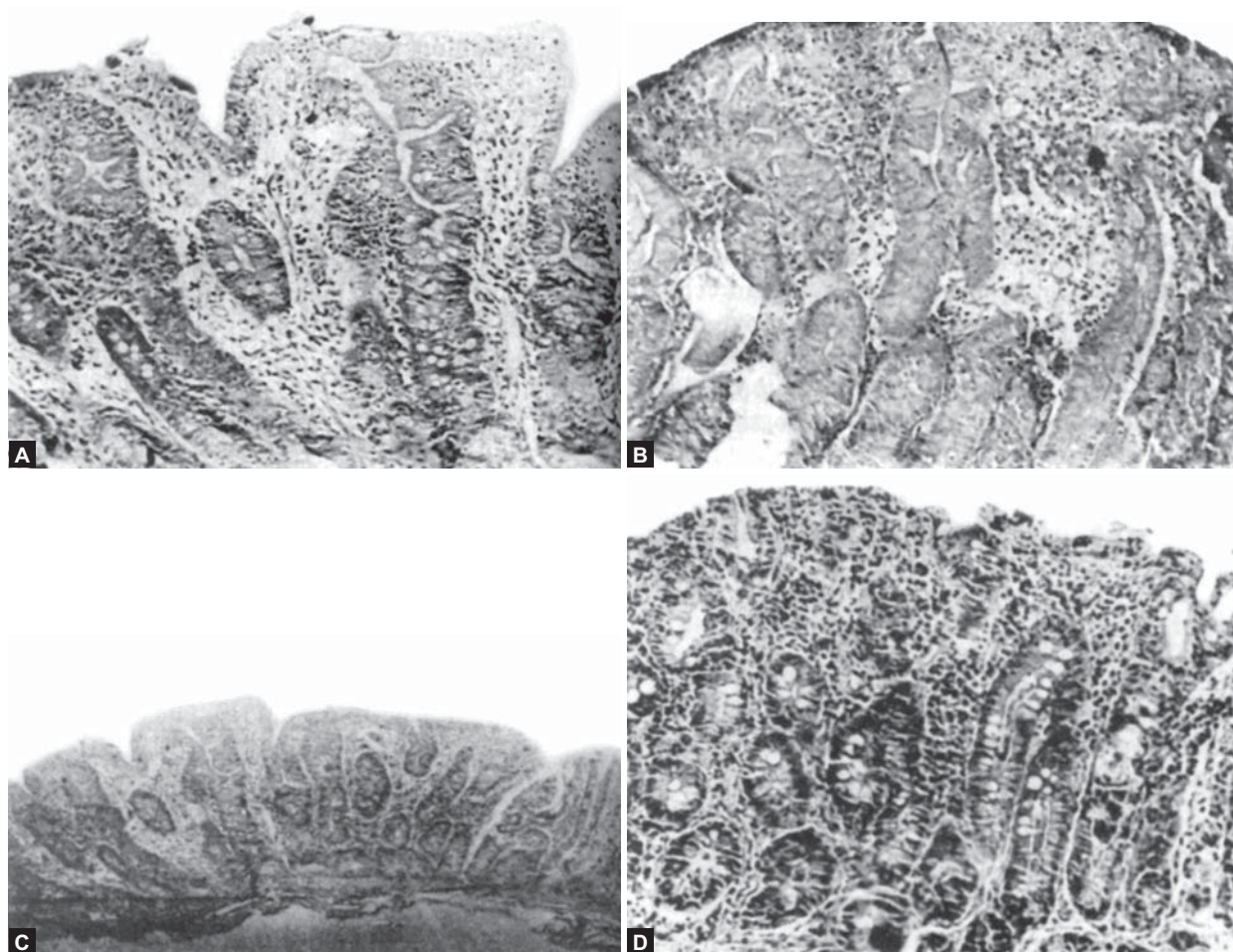
- Is there a family history of chronic diarrhea (CF, CD, hereditary lactose intolerance)?
- Is there any history of intolerance to an item of food, i.e. wheat, barley, rye, oat (CD) or milk (lactose intolerance)?
- Was the child failing to thrive from early infancy or started suffering from growth failure after introduction of a solid food? The latter situation is very much suggestive of CD.
- How is the appetite? It is generally increased in CF and in some children suffering from giardiasis. In CD, it is almost always poor. Mothers of celiacs often express surprise 'as to how children who eat so little can pass such voluminous stools'.
- Does the mother feel that the child eats like a glutton but, despite all that, he has not been growing well? This strongly suggests CF. We have encountered this situation in some children suffering from symptomatic giardiasis as well.
- What do the stools look like? Large, pale, frothy and very foul-smelling stools are highly suggestive of steatorrhea. Characteristically white, fatty stools with plenty of undigested material are most often a feature of giardiasis.
- Was the persistent diarrhea preceded by an attack of acute gastroenteritis? The situation is highly indicative of secondary lactose intolerance. This condition is fairly common and the stools in it are watery, profuse, accompanied by excess of flatus and have extremely foul smell. The perianal area appears raw and red in a large majority of these children.
- **Stool microscopy:** Microscopic examination of stools for evidence of parasitic infestations is of definite value. At least three meticulous stool examinations on successive days are essential before one rule out the presence of intestinal infestation. The presence of numerous large fat globules, after staining with Sudan-3 or eosin, is indicative of steatorrhea. However, this is a rough screening test
- **Daily stool fat:** Chemical examination of stools for fat content is the next important investigation.

The child is placed on a diet that provides at least 50g of fat per day over a period of 6 days. During the last 3 days all the stools passed by the child are collected and analyzed chemically. The 24-hour fat excretion is calculated. The mean fat excretion in normal Indian infants and children is 2.32 ± 0.73 g. A fat excretion of more than 5 g/24 hours is regarded as indicative of steatorrhea. Stool fat can also be measured by a semiquantitative simple, cheap and accurate method, **steatocrit**. It is a method of microcentrifugation of fecal homogenate.

- **D-xylose test:** In older children, D-xylose excretion in a 5-hour urine sample, after administration of the pentose in a dose of 1.0 g/kg of BW, dissolved in water, is estimated. An excretion of <20% indicates malabsorption. Infants and young children present difficulties in collection of urine. D-xylose tolerance test is, therefore, preferred in their case. Here, D-xylose is administered in the same dose and blood samples are taken at 0, 30, 60, 90 and 120 minutes by finger prick. Estimation of the pentose in these small samples is done by a micromethod. The peak level of <30 mg% is considered indicative of absorptive defect of the small bowel. A child with steatorrhea but normal D-xylose test is said to be suffering from steatorrhea of

nonenterogenous origin as is the case with CF and, in our experience, with giardiasis also

- **Endoscopic/peroral jejunal biopsy:** In view of the nonspecific results obtained from this investigation, its use may be reserved for difficult cases. Only in a few conditions like intestinal lymphangiectasia, abetalipoproteinemia, amyloidosis and intestinal lymphoma is the intestinal histology pathognomonic. In CD, endemic tropical sprue, protein energy malnutrition (PEM), iron deficiency anemia and ancylostomiasis, similar types of villous atrophy occur and differentiation on the basis of histologic changes is nearly impossible (Figs 29.9A to D).
- **Radiology:** Barium meal examination, using a non-flocculable medium may reveal abnormalities like intestinal dilatation, flocculation, segmentation and atypical mucosal pattern. These are indicative of malabsorption but fail to differentiate one condition from another, especially the ones that are responsible for most of the tropical malabsorption in infants and children. This investigation is of value in detecting anatomic defects.
- **Other investigations:** Schilling test, sweat chloride estimation, tryptic activity, lactose tolerance test, etc. may be performed under special circumstances,



Figs 29.9A to D: Peroral jejunal biopsies showing significant villous atrophy in children suffering from celiac disease, protein energy malnutrition (PEM), iron deficiency and hookworm infestation.

Box 29.10**Usefulness of jejunal biopsy in evaluation of chronic diarrhea/malabsorption**

- **Pathognomonic**
 - Intestinal lymphangiectasia
 - Abetalipoproteinemia
 - Amyloidosis
 - Intestinal lymphoma
 - **Parasites:** *Giardia lamblia* (sometime)
 - Agammaglobulinemia
 - ♦ Crohn's disease
 - ♦ Microvillous atrophy
 - ♦ Tufting enteropathy
- **Nonspecific**
 - Celiac disease
 - Endemic tropical sprue
 - Iron deficiency
 - Ancylostomiasis
 - ♦ Cow milk protein intolerance
 - ♦ Severe malnutrition
 - ♦ Radiation enteritis

depending on the individual merits of a case. These, like jejunal biopsy (Box 29.10) and radiology, need not to be done in every child suffering from chronic diarrhea/malabsorption.

Despite the fact that the list of causes responsible for malabsorption is rapidly expanding, in practice only a few of the conditions appear to monopolize the situation. In our experience, stool fat signifying mild to moderate steatorrhea is usually indicative of PEM, IDA or intestinal parasitic infestation. Gross steatorrhea is generally due to CF, CD or tropical sprue.

The diagnosis of CF is best confirmed by sweat chloride estimation (sweat chloride is very high in this condition, always above 60 mEq/L) and tryptic activity.

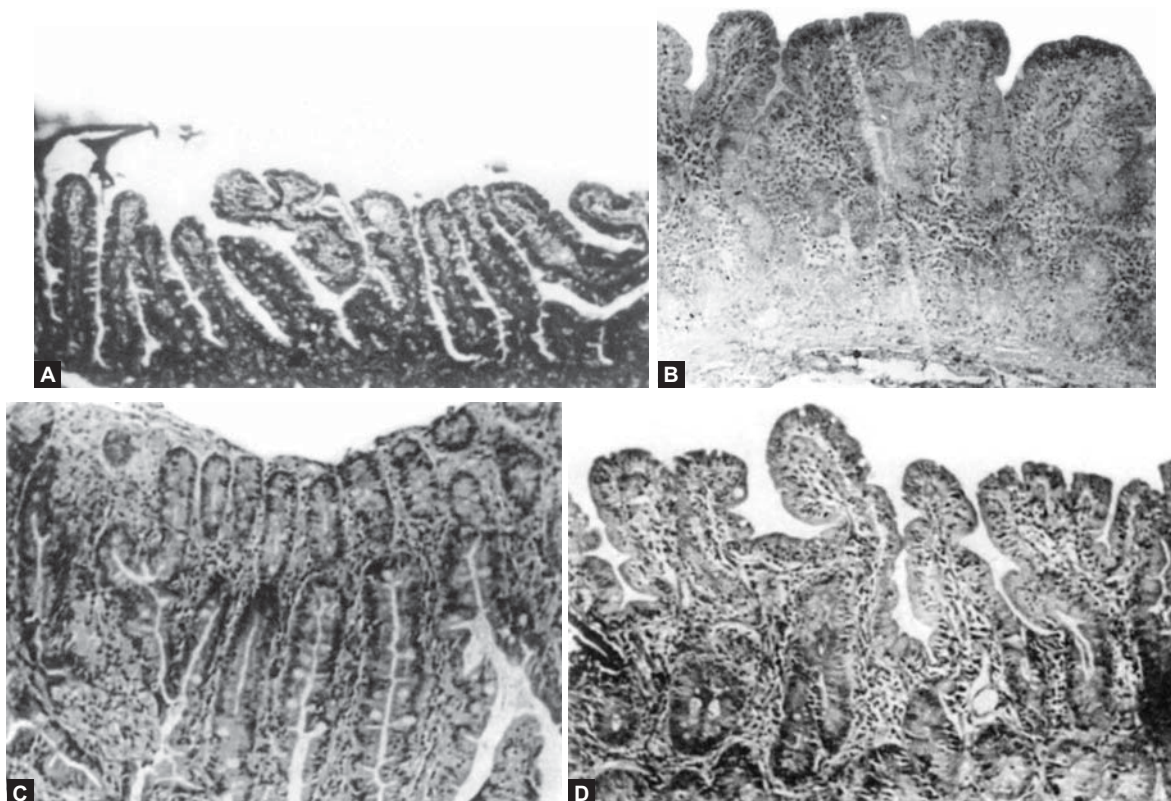
A patient with gross steatorrhea, in whom the diagnosis of CF has been excluded, may be put on gluten-free diet. If he shows amelioration of symptoms, this regimen is continued and absorptive tests (and jejunal biopsy, if done earlier) are repeated after a period of 10–12 weeks. If found normal, the patient is challenged with gluten to see if the intestinal abnormality returns. This is now considered adequate to confirm the diagnosis of CD. If, on the other hand, 3 months of gluten-free diet fails to benefit, the patient's record is reviewed to find, if he could be a case of tropical sprue. A Schilling test is indicated in this situation. If it is abnormal, he should be put on folic acid and/or tetracycline therapy. Symptomatic control of diarrhea, as the diagnostic tests are in progress, is desirable.

Lastly, it is worthwhile to have a clear idea about the pattern of chronic diarrhea/malabsorption in a particular region. This, together with an individualized approach and an adequate follow-up, solves a vast majority of the diagnostic problems (Figs 29.10A to D).

Fig. 29.12 presents algorithmic approach to management of chronic diarrhea in pediatric practice.

CELIAC DISEASE**(Gluten-Induced Enteropathy)**

It is one of the most common causes of malabsorption in the West. Until recently, it was believed to be practically



Figs 29.10A to D: Peroral jejunal biopsies from the patients in Figs 29.9A to D after treatment. Note that the appearances are comparable to the normal as shown in Fig. 29.11.

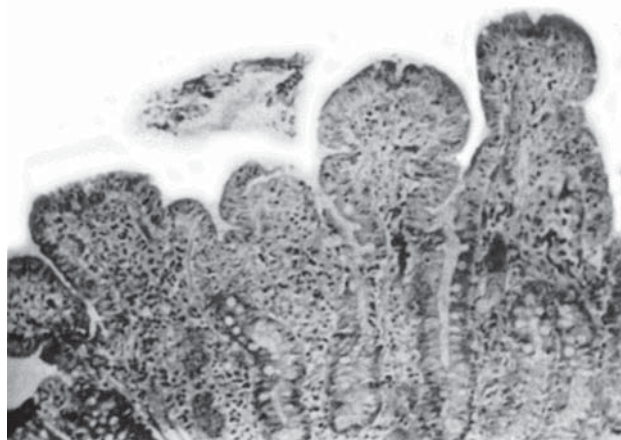


Fig. 29.11: Peroral jejunal biopsy showing normal histological appearance.

nonexistent in the oriental population. Since 1960s, it has emerged as one of the top causes of chronic diarrhea/malabsorption in wheat-eating population in India as well.

Etiopathogenesis

It is an abnormal response to the gliadin fraction of gluten present in wheat, barley, rye and oat. Varying degree of villous atrophy, resulting in absorptive defect, is an essential pathologic lesion. Without dietary manipulation, the small intestinal mucosal damage is permanent. Elimination of gluten from diet, however, leads to disappearance of the changes. Reintroduction of gluten causes their reappearance. This characteristic feature of CD has earned it, such descriptive names as **gluten-sensitivity** and **gluten-induced enteropathy**. The so-called **transient gluten**

sensitivity that has been reported in several disorders is, therefore, strictly speaking, not to be included under this heading.

Clinical Features

The disorder generally manifests a few months after the introduction of gluten-containing foods—often a wheat preparation in the feeding program. Chronic diarrhea—with large, pale, highly foul-smelling stools which stick to the pangrowth failure, anemia and other vitamin and nutritional deficiencies, abdominal distention, irritability and anorexia are the usual presenting features (Figs 29.13A and B).

Diagnosis

In the presence of above mentioned clinical profile, the diagnosis of CD must be seriously considered.

Conventional Approach

To establish existence of malabsorption, daily stool fat excretion should be biochemically determined. D-xylose test is another useful diagnostic tool. Histological abnormality of the small intestinal mucosa can be demonstrated by endoscopic/peroral intestinal biopsy (Table 29.13). Responses to removal of gluten from diet and, latter, to gluten challenge are needed to establish the diagnosis.

Two immunoglobulin A (IgA) dependent tests are currently recommended:

1. **Serum IgA against tissue transglutaminase (tTG)**. It is an ELISA based test with a very high sensitivity as well as specificity varying between 90–100%

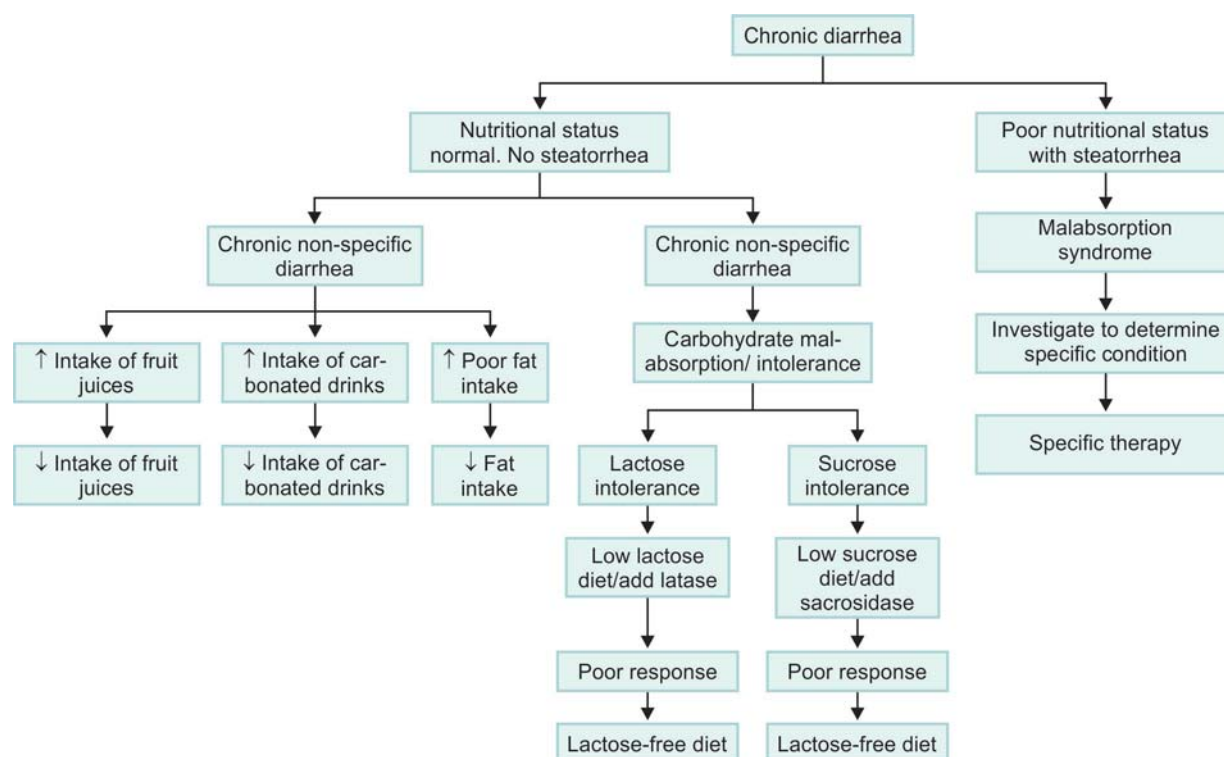


Fig. 29.12: Algorithmic approach to pediatric chronic diarrhea.



Figs 29.13A and B: Celiac disease. Note the growth retardation, abdominal protuberance and irritability in this 3-year-old girl who suffered from chronic diarrhea since the age of 7 months with investigations consistent with celiac disease.

Table 29.13: Marsh criteria of histological changes in small intestinal biopsy in celiac disease

Grade	Histological picture	Significance
1	Normal	—
2	Infiltrative with increased intraepithelial lymphocytes	Nonspecific but compatible with CD
3	Hyperplastic, i.e. grade 1 changes + hyperplastic crypts	Characteristic of CD
4	Hypoplastic (total villous atrophy + hypoplastic crypts)	Characteristic of CD

Abbreviation: CD, celiac disease.

2. **Serum IgA antiendomysial antibody (EMA).** It is based on immunofluorescence technique, has an equally high sensitivity and specificity. However, it is expensive and not easily available.

Antigliadin antibodies (AGA) and antireticulin antibodies (ARA) are no longer recommended in view of their high false positivity. Serology, though a very important test for the diagnosis of CD, needs to be supported by an abnormal intestinal biopsy and response to gluten-free diet. Box 29.11 lists the modified diagnostic criteria for CD as per the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN). The major change from the old criteria is that gluten-challenge (an essential criteria earlier) is no longer required. Coexistence of CD with CF is known. Such a situation causes difficulties in arriving at the exact diagnosis.

* GFD means not just wheat-free but also barley, rye and oat-free diet. Oat does not contain gluten, but the way it is stored renders it susceptible to contamination with gluten-containing items.

Box 29.11

ESPGAN modified criteria for diagnosis of CD in children

- Clinical profile in keeping with diagnosis:
 - Jejunal biopsy in keeping with the diagnosis as such or with serology.
 - Unequivocal response to gluten-free diet within 12 weeks of its introduction.

Abbreviations: ESPGAN, European Society of Pediatric Gastroenterology and Nutrition; CD, celiac disease.

Treatment

The cornerstone of management is **gluten withdrawal** from diet which has to be strictly enforced. Gluten-free diet (GFD)* latter has got to be a life-long measure. Attention to good nutrition with supplements of iron and folic acid is important.

GFD leads to a prompt improvement in appetite, weight gain, and control of chronic diarrhea, etc. Six months of gluten-free diet should be followed with TTG estimation for fall in titers to show compliance is adequate. Repeat biopsies (post-therapy or postgluten challenge) are no longer recommended.

Prognosis

Untreated CD carries enhanced risk of:

- Lymphoma
- Cancers
- Autoimmune disorders
- Osteoporosis.

CYSTIC FIBROSIS

(Mucoviscidosis)

A common disorder in the Western countries, its occurrence in India has only recently been recognized.

Etiopathogenesis

Cystic fibrosis is a genetic disorder involving the **exocrine glands**—not just the pancreas, but the sweat glands as also the glands in the liver as well. As a rule, intestinal mucosa is normal. Steatorrhea is, therefore, of extraintestinal origin.

Clinical Features

Chronic/recurrent diarrhea and recurrent respiratory infections—especially since early infancy—FTT despite exceptionally good appetite and multiple nutritional deficiencies are the common presenting features (Fig. 29.14). Stools are characteristically steatorrheic but may be loose. An obstinate catarrhal cough or frog in the throat may be present ever since the first weeks of life. Abdominal distention, a palpable liver, clubbing, higher incidence of rectal prolapse and nasal polyps, and pseudotumor cerebri are the other findings.

A noteworthy observation by the mother may be a line of salt on the forehead after sweating or 'the baby tastes



Fig. 29.14: Cystic fibrosis. This 8-month-old baby had recurrent diarrhea and respiratory infections since birth. His sweat chloride was 256 mEq/L.

salty when kissed'. At times, CF may manifest at birth as meconium ileus, meconium peritonitis or ileal atresia.

Diagnosis

When clinical picture arouses suspicion, fat balance studies to establish steatorrhea and D-xylose test to establish that steatorrhea is not enterogenous in origin are indicated. Poor tryptic activity lends support to the clinical diagnosis. But, a high sweat chloride* (in no case <60 mEq/L) is a must to confirm the diagnosis. Sweat chloride test is considered the gold-standard for diagnosis of CF. Deoxyribonucleic acid (DNA) testing for CFT mutations is now available.

Fetal screening of CF (F 508) is not feasible. Very infrequently, CF may coexist with CD, posing difficulties in arriving at the diagnosis.

Treatment

- Every child with proved CF should receive pancreatic enzymes replacement therapy (PERT). PERT effectiveness is enhanced when administered in enteric-coated microspheres form (mixed with acid foodstuff (say sour fruit or fruit juice). Its dose is calculated either by weight of the child or by weight of the fat consumed.
- Antibiotics are indicated to control respiratory infections.
- Maintenance of nutrition and symptomatic measures are indeed important.
- Gene therapy (DNase), both bovine and human, is now available for CF.

Complications

These include bronchiectasis, systemic amyloidosis, cor pulmonale and cirrhosis. One-half of the CF subjects



Fig. 29.15: Endemic tropical sprue. Note the remarkable growth retardation in this 9-year-old child with chronic diarrhea and moderate dimorphic anemia.

who reach beyond 20 years, develop CF-related diabetes (CFRD) due to a combination of insulin deficiency and resistance.

ENDEMIC TROPICAL SPRUE

Contrary to the time-honored belief that the condition affects adults only, its occurrence in childhood is being increasingly recognized now.

A typical case is a grown-up child with chronic diarrhea, malabsorption, considerable malnutrition and anemia (Fig. 29.15). Steatorrhea is usually moderate to gross. Partial or subtotal villous atrophy is present. D-xylose test shows poor intestinal absorption. Schilling test is almost always abnormal, indicating that the intestinal mucosal atrophy and absorptive dysfunction are not limited to the upper gut but are present in the ileum too. These patients do not respond to gluten-free diet or to gluten challenge as is remarkable of CD.

Endemic tropical sprue is considered a sort of folic acid deficiency. Many patients show encouraging response to 10–20 mg/day of folic acid. A group of patients may need a prolonged course of tetracyclines, favoring an infective etiology. Yet, others may have to be given both, folic acid and tetracyclines.

PROTEIN-LOSING ENTEROPATHY

The term refers to excessive loss of plasma proteins (predominantly albumin) into the gut.

Etiology

A number of diseases may have associated protein-losing enteropathy (Box 29.12).

* Sweat chloride may be high (not as much as in CF) in other conditions such as malnutrition, hypothyroidism, hypoparathyroidism, nephrogenic diabetes insipidus, adrenal insufficiency, pancreatitis, G6PD deficiency, familial cholestasis, mucopolysaccharidosis, etc.

Box 29.12 Etiology of protein-losing enteropathy

- **Gut**
 - **Stomach:** Giant hypertrophic gastritis
 - **Small gut:** Malabsorption syndrome
 - **Large gut:** Dysentery, ulcerative colitis, Hirschsprung disease.
- **Cardiac**
 - CCF, ASD, constrictive pericarditis
- **Miscellaneous**
 - Immunodeficiency.

Abbreviations: CCF, congestive cardiac failure; ASD, atrial septal defect.

Clinical Features

Besides the clinical picture of the primary disease, the patient may have poor weight gain, hypoproteinemic edema (with or without chylous ascites), anemia (especially megaloblastic) and vitamin deficiency signs (especially those of fat-soluble vitamins).

Diagnosis

Plasma albumin is usually below 2.5 g/dL. Nutritional, hepatic and renal causes of hypoproteinemia need to be excluded before labeling a case as that of protein-losing enteropathy. For establishing the diagnosis, measurement of spot stool alpha-1-antitrypsin (unlike albumin it resists digestion) level is of value.

Treatment

Treatment is essentially that of the primary underlying disorder. If there is gross hypoproteinemia from severe losses, albumin infusions may be of temporary benefit.

CARBOHYDRATE MALABSORPTION

It may be of two types—(1) disaccharide malabsorption, and (2) monosaccharide malabsorption.

Disaccharide Malabsorption

It may be primary or secondary:

- In **primary disease**, which is very rare, there is congenital deficiency of one or more of the disaccharidase enzymes (lactase, isomaltase, invertase, maltase) in the brush border of the small bowel epithelium.
- In **secondary disease**, the enzyme deficiency results from such conditions as acute gastro enteritis, PEM, cow milk protein (CMP) allergy, CF, gluten-induced enteropathy or drugs like neomycin.

Clinical Features

Watery diarrhea with only little solid matter, acid character of stool, excoriation of the perianal area and buttocks, abdominal distention and pain are noticed. The abdominal cramps are particularly a feature of lactose intolerance in older children and result from excessive gas production.

Diagnosis

- Character of diarrhea and circumstances of its onset.
- Low pH of stools (under 6) while the patient is on modest dietary intake of the offending sugar(s).

- Presence of reducing substances in stools.
- Disaccharide (usually lactose) tolerance test.
- Breath test involving measurement of H^+ .
- Barium meal—the suspected sugar is added to a barium meal. Defect in its absorption causes fluid retention in intestinal lumen, intestinal hurry and coarsening of the mucosal folds.
- Endoscopic/peroral jejunal biopsy for assay of the enzymes offers the most definitive diagnosis.

In clinical practice, diagnosis is more often confirmed by response to withdrawal of the offending sugar from the diet rather than by cumbersome investigations.

Treatment

It is by giving low-disaccharide diet. Soya milk is a good substitute for milk in case of lactose intolerance. As the child grows, symptoms often become less severe in congenital deficiency. In acquired one, the phenomenon is in any case transient and subsides in due course, particularly with the restriction of the sugar.

Monosaccharide Malabsorption

- A rare congenital disorder, it is being increasingly reported in association with PEM, gastroenteritis, chronic diarrhea, gluten-induced enteropathy, or following surgery.
- Treatment consists of excluding glucose and galactose from diet. A period of intravenous feeding is usually indicated in serious cases.
- Reintroduction of the sugars should be cautious.

COW MILK PROTEIN INTOLERANCE**(Cow Milk Protein Hypersensitivity/Allergy)**

About 1–2% of infants may have hypersensitivity to cow milk.

Clinical Features

- Vomiting, diarrhea (usually watery), colic, rash (infantile eczema or urticaria), rhinitis, otitis media, chronic cough with wheeze (just as in bronchial asthma), anemia and poor weight gain.
- Eosinophilia, glucosuria, sucrosuria, lactosuria, aminoaciduria, renal tubular damage, acidosis and pulmonary acidosis may occur in some cases.
- Smear from rectal mucus shows eosinophils.

Withdrawal of cow milk is followed by disappearance of the manifestations. Its reintroduction leads to reappearance of the symptoms within 48 hours.

Etiology

Allergy to beta-lactoglobulins appears to be the operative cause in large majority of the cases. Allergy to casein, lactalbumin, bovine serum globulin and bovine serum albumin may also be present. Remember, the disorder is no longer considered a sort of lactose intolerance due to deficiency of lactase in the small intestinal mucosa.

Treatment

Management consists of omitting cow milk from the feeding regimen. Soya milk or goat milk may well be a good substitute. When the infant approaches the age of 9 months, cow milk may be introduced drop by drop, increasing the amount everyday until the desired intake is reached.

Alternatively, if rapid reintroduction is desired, cow milk may be given under the shield of 10 mg of prednisolone daily. Once milk is tolerated, prednisolone should be slowly tapered off to zero dose.

ACRODERMATITIS ENTEROPATHICA

(Brandt Syndrome)

This is a familial disorder with autosomal recessive inheritance and with unique cocktail of clinical manifestations.

Etiology

The cause is zinc deficiency secondary to malabsorption of zinc.

Clinical Features

The condition, manifesting at the time of weaning, is characterized by chronic diarrhea (at times, together with steatorrhea), symmetrical rash or vesiculobullous, eczematous, dry, scaly or psoriasiform lesions (Fig. 29.16), paronychia, nail dystrophy, loss of hair (alopecia), stomatitis and glossitis. The skin lesions are most marked over the mucocutaneous junctions (buttocks, around the anus and mouth), face (cheeks) and extremities (knees, elbows). Blepharitis, conjunctivitis and photophobia are the frequent ocular accompaniments. Superadded *Candida albicans* infection may modify the clinical profile. Left untreated, it is accompanied by FTT.

Differential Diagnosis

Acrodermatitis enteropathica needs to be differentiated from a similar syndrome resulting from long-term total parenteral nutrition (TPN) (unsupplemented with zinc) and in chronic malabsorption, advanced PEM, CF, maple



Fig. 29.16: Acrodermatitis enteropathica. Note the symmetrical rash and alopecia in an infant with diarrhea.

syrup urine disease, organic aciduria, essential fatty acid deficiency, biotinidase deficiency and methylmalonic acidemia. **573**

Diagnosis

It is by and large clinical. Serum zinc level and alkaline phosphatase activity are reduced. Small intestinal biopsy demonstrates Paneth cell inclusions with parakeratosis and pallor of the upper epidermis.

Treatment

Zinc, 1–2 mg/kg/day (elemental) in divided doses, gives dramatic response with improvement in diarrhea and prompt healing of skin lesions. With the availability of zinc for therapeutic use, diiodohydroxyquin which was supposed to yield good results but was likely to cause optic neuritis in infants is no longer employed.

INFLAMMATORY BOWEL DISEASE

Definition

Inflammatory bowel disease is defined as a chronic inflammatory disease of the gut with overwhelming gastrointestinal presentation and some systemic manifestations. Three types are recognized:

1. **Ulcerative colitis:** Only colon is involved with continuous lesions.
2. **Crohn's disease:** The whole of gut is involved with discontinuous lesions with normal intervening mucosa (skip lesions).
3. **Indeterminate colitis:** Nonspecific manifestations not fitting into ulcerative colitis or Crohn's disease.

Ulcerative Colitis

It is characterized by recurrent bloody diarrhea and inflammation of the colonic mucosa beginning in childhood and adolescence and showing peak age at 15–25 years.

Etiology

The disease is now believed to be an immunologically mediated reaction triggered in a genetically vulnerable host. Identical twins, close family members, patients of ankylosing spondylitis and Turner syndrome have greater susceptibility to the disease. Incidence in Jews is 2–4 times greater than in general population.

Clinical Features

- Bloody diarrhea with copious mucus, fecal urgency, tenesmus and lower abdominal pain, especially just before defecation, anorexia, weight loss, FTT and nutritional deficiency and growth retardation.
- Occasionally, the onset may be acute with fulminant bloody diarrhea, high pyrexia and progression to peritonitis and even perforation.
- Abdominal examination reveals distention and tenderness, especially along the left side. Bowel sounds are exaggerated.
- Rectal examination may reveal fissures and, at times, fistulae and abscesses.

- 574 ■ Extraintestinal manifestations (less frequent in pediatric ulcerative colitis) include arthritis, erythema nodosum, pyoderma gangrenosa, iritis, hepatitis, clubbing, peripheral hypoproteinemic edema, phlebitis, hemolytic anemia, etc.
- The disease is characterized by recurrent exacerbations, most subjects remaining asymptomatic and well during remissions that may stretch over months to years.

Investigations

In addition to detailed history (including family and treatment history), clinical examination (including rectal examination for tags, fissures and fistula), and such tests as complete blood picture, serum protein, stool examination for occult blood, C-reactive protein (CRP), etc. the following specific investigations should be done:

- Barium enema, less sensitive than colonoscopy, reveals diffuse distal lesion that may extend proximally to involve the whole colon only in later stages of disease
- Colonoscopic examination reveals that rectal and distal colonic mucosa is inflamed, granular and very friable; active bleeding may be there (Fig. 29.17). Ulcers, unusual in pediatric ulcerative colitis, are diffuse.
- Serology—it is positive for perinuclear antineutrophil cytoplasmic antibody (p-ANCA).

It is of value to evaluate the small intestine as well by barium meal follow through, computed tomography (CT) enteroclysis or magnetic resonance (MR) enterography for ascertaining extent of disease. Involvement of small intestine favors diagnosis of Crohn's disease.

Differential Diagnosis

It is from:

- Chronic intestinal infections such as *Campylobacter jejuni*, *Yersinia enterocolitica*, *Edwardsiella tarda*, *Aeromonas hydrophila*, *Plesiomonas shigelloides*, *Mycobacterium tuberculosis*, *E. histolytica*, *Cryptosporidium*, *Isospora belli* and *Cytomegalovirus*

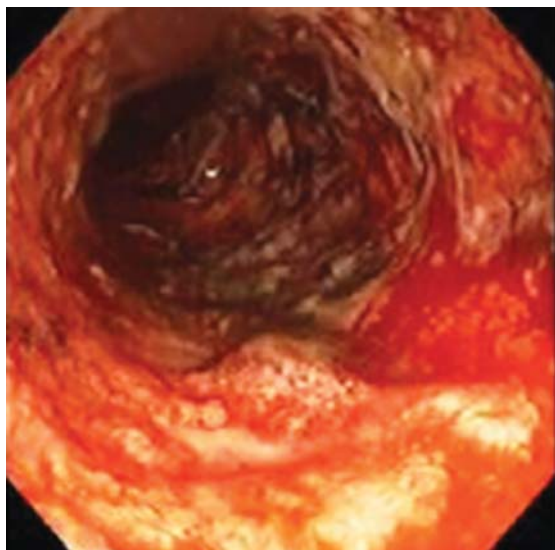


Fig. 29.17: Ulcerative colitis. Colonoscopy showing severe colitis with denuded mucosa and active bleeding. Such a severe ulcerative colitis is an indication for resection of the colon.

- Crohn's disease
- Necrotizing enterocolitis
- Intolerance of dietary protein
- Hemolytic uremic syndrome
- Hirschsprung disease, etc.

Treatment

- **Diet:** It is by and large supportive with special attention to the nutrition, including supplements of vitamin D and calcium to prevent osteoporosis
- **Drugs:** To reduce inflammatory activity, currently recommended agents are:
 - 5-aminosalicylic acid (5-ASA)
 - Steroids
 - Cyclosporine
 - 6-MP (mercaptopurine)
 - Azathioprine
 - Methotrexate
 - Infliximab (monoclonal antibodies against tumor necrosis).
- **Adjuvant therapy:** In the wake of some recent reports, probiotics may be considered as an adjuvant therapy for added benefit in inducing and maintaining remission
- **Surgery:** Surgical resection of the whole colon cures the disease. Its indications are:
 - Acute colitis not responding to conservative measures
 - Poorly controlled hemorrhage
 - Intestinal perforation
 - Megacolon
 - Intestinal obstruction
 - Abscess.

Complications

These include hemorrhage, perforation of colon, megacolon and colonic cancer (3% risk in first decade and 20% in subsequent years).

Crohn's Disease

It is also termed as regional ileitis, granulomatous enterocolitis, it has similar etiology, age incidence and certain other features as in ulcerative colitis, is characterized by segmental transmural bowel involvement, distal ileum and colon being most commonly affected.

Clinical Features

These include crampy abdominal pain and diarrhea that may be accompanied in one half of the patients by pyrexia, malaise, anorexia, growth failure and arthralgia or arthritis. Chronic perianal lesions like skin tags, fissures, fistulas and abscesses even in an asymptomatic child should be considered as early signals of Crohn's disease. Extraintestinal manifestations are more frequent in Crohn's disease than in ulcerative colitis.

Diagnostic Investigations

- Upper gastrointestinal endoscopy with biopsy which reveals an inflammatory lesion with polymorphonuclear infiltration and crypt abscesses.

- Barium contrast roentgenograms reveal segmental distribution, irregular mucosa or a cobblestone-like pattern, thickened bowel and enteric fistulae.
- Rectal biopsy shows typical noncaseating granuloma with transmural inflammation.
- Fiberoptic colonoscopy rather than conventional sigmoidoscopy defines the colonic involvement. The so-called **skip lesions** characterized by ulceration with normal intervening mucosa spread throughout the gut.

Treatment

It is primarily supportive with special emphasis on maintenance of good nutrition and emotional support to the patient and the family. For acute exacerbations, prednisolone needs to be given for 6 weeks and then tapered gradually over 8–12 weeks period.

In severe exacerbations, it may be given in conjunction with azathioprine. Sulfasalazine, for colonic Crohn's disease, metronidazole for cases with fistulae and severe perianal problems, methotrexate and cyclosporine for some severe cases are also recommended.

Surgical resection is of less value than in ulcerative colitis. The current recommendation is to resect as little as possible (scar removal) for improved results.

Prognosis

Prognosis is rather poor. Though incidence of intestinal cancer is much < in ulcerative colitis, 1–2 decades after the onset of the disease, most subjects with Crohn's disease develop obstructive problems in relation to the intestinal lumen, especially in the ileal disease.

Crohn's Disease Versus Ulcerative Colitis

Distinguishing features between Crohn's disease and ulcerative colitis are listed in Table 29.14.

FUNCTIONAL GASTROINTESTINAL DISORDERS

The term, **functional gastrointestinal disorders (FGIDS)**, is an umbrella that includes a spectrum of disorders characterized by a combination of symptoms that are chronic or recurrent and are not explained entirely with current structural or biochemical investigations.

The use of the term, functional, implies that many of the symptoms may accompany normal development or may be a response to otherwise normal internal or external cues. Earliest description of a FGID was given by Apley who coined the term **recurrent abdominal pain** in 1958 which was revised by the Rome Pediatric Working Group on functional gastrointestinal disorders in 2006.

CHRONIC ABDOMINAL PAIN

(Recurrent Abdominal Pain)

Some 5–10% of school going children suffer from chronic abdominal pain (CAP)—the new semantic for recurrent abdominal pain (RAP). In quite a proportion of them, the etiologic diagnosis remains elusive despite a battery of investigations.

Table 29.14: Distinguishing features of Crohn's disease and ulcerative colitis

Features	Crohn disease	Ulcerative colitis
Bloody diarrhea/rectal bleed	Infrequent	Common
Abdominal pain	Common	Variable
Abdominal mass	Common	Absent
Failure to thrive/growth failure	Common	Variable
Perianal disease	Common	Infrequent
Rectal involvement	Infrequent	Invariably present
Stomatitis	Common	Rare
Colonic involvement	Variable (present in over one-half subjects)	Always present
Ileal involvement	Common	Absent
Strictures	Common	Unusual
Fistulas	Common	Unusual
Fissures	Common	Absent
Toxic megacolon	Absent	Present
Cancer risk	Enhanced	Greatly enhanced
Histopathology	Granuloma	Transmural; cryptitis, crypt abscesses
Typical lesions	Skip lesions	Continuous lesions

Definition

Currently, CAP is defined as the abdominal pain that is spread over a period of 3 months or more. Whether it is recurrent with pain-free intervals or occurs every day has no bearing on the present definition.

This definition replaces the Apley's definition that described RAP as abdominal pain that is severe enough to disturb daily activities, occurring at least three times over a 3-month period.

Classification/Types

Chronic abdominal pain may be classified into two major categories—1. nonorganic and 2. organic.

1. Nonorganic chronic abdominal pain:

- It may be functional (psychogenic) or secondary to irritable bowel syndrome (IBS), 3-months colic, nonulcer dyspepsia, etc.
- In case of functional CAP, the pain is periumbilical, nonspecific and inconsistent. There, usually, is a secondary gain pattern (usually skipping the school) and the child manages to seek the attention of the parents, may the whole household
- There is often evidence of parental conflict, disturbed interpersonal relationship and parent(s) frequently complaining of abdominal or other bodily pains.

Box 29.13 lists classical pain pattern in nonorganic CAP. Rome II Group defines **functional abdominal pain syndrome** as 12-week of continuous or nearly continuous abdominal pain in a school-going child or adolescent with no or occasional relationship with physiological

Box 29.13**Classical pain pattern in nonorganic chronic abdominal pain**

- Gradual onset
- Periumbilical pain
- Paroxysmal with variable severity
- No or vague relationship with food or defecation
- Clustering of pain
- Failure to clearly describe location and nature of pain by the child/parents.

events like eating, defecation, and menstrual cycles. Some interference with daily functions may be seen. CAP in this case should neither be malingering nor fit into any other known functional GI disorder (functional dyspepsia, IBS, abdominal migraine, aerophagia).

2. **Organic recurrent abdominal pain**

- It may be secondary to conditions in relation with GIT (gastroesophageal reflux, intestinal parasitosis, chronic constipation, lactose intolerance, food allergy or lactose intolerance, Crohn's disease, ulcerative colitis, *Helicobacter pylori* infection, recurrent intussusception, chronic appendicitis, inguinal or abdominal wall hernia), gallbladder (cholelithiasis, choledochal cyst), pancreas (recurrent pancreatitis), genitourinary tract, urinary tract infection, urolithiasis, hydronephrosis), CNS (abdominal migraine), hemopoietic system (sickle cell crisis, Henoch-Schönlein purpura)
- The pain invariably is away from the umbilicus, usually in the dermatone that supplies innervation to the involved viscera. It tends to be constant and consistent, localized or diffused
- Rebound tenderness may be present
- Evidence of the primary disease supports the diagnosis of organic RAP.

Box 29.14 lists classical pain pattern in organic CAP.

Diagnosis

Clinical Work-up

A detailed clinical work-up is mandatory in the evaluation of the child with RAP. Information should also be obtained

Box 29.14**Classical pain pattern in organic chronic abdominal pain**

- Pain away from umbilicus
- Localized pain
- Associated fever
- Associated weight loss
- Radiating pain
- Well-defined pain, say stabbing, burning sensation
- Pain severe enough to awaken the child from sleep
- Tenderness
- Organomegaly
- Anemia
- Urinary symptoms
- High ESR/CRP
- Arthralgia, rash or purpura.

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Box 29.15**Stepwise investigative protocol for CAP**

- **Level 1:** Blood, urine and stool (at least on 3 successive days). Extended investigations include screening for tuberculosis, LFT, RFT, S. amylase and lipase, X-ray of abdomen and chest and ultrasonography
- **Level 2:** Further investigations should depend on the clues obtained from the clinical work-up and/or initial investigations. These include:
 - GI contrast studies
 - Upper GI endoscopy is important for confirming GER
 - Colonoscopy.
- **Level 3:** EEG for abdominal epilepsy, cyclic vomiting syndrome
 - Specific tests for porphyrias, lead poisoning, food allergy, lactose tolerance, collagen vascular disorders, motility disorders, etc.

Abbreviations: LFT, liver function test; RFT, renal function test; S. amylase, serum amylase; GI, gastrointestinal; GER, gastroesophageal reflux; EEG, electroencephalogram; CAP, chronic abdominal pain.

on child's emotional status, interpersonal relationship with parents, siblings, school teacher and peers, school performance, etc.

Investigative Work-up

A structured stepwise approach is needed, starting with simple investigations and moving on more sophisticated if the need be (Box 29.15).

Treatment

Management is dictated by the diagnosis. In a proportion of cases, no specific diagnosis may be forthcoming in spite of investigations. It is in order to reassure them and carry deworming effective for the common infestations prevalent in the area. Deworming may well be repeated once in 3 months.

In psychogenic RAP, all efforts must be made to alleviate the child's as well as parental anxiety and tension—sometime, if the need be, with assistance from a psychiatrist.

CONSTIPATION

Constipation is a common pediatric problem responsible for physical and psychological morbidity and poor quality of life (QoL).

As a normal physiological phenomenon, most children after infancy (when stool frequency is around 4+/day) slowly settle to a frequency of a single motion/day by 4 years. Some normal children may pass a normal motion not daily but every 3–4 days.

Definition

It is defined as passage with difficulty of hard, dry stools accompanied by considerable discomfort and/or distress to the child. More than duration, it is the troublesome evacuation that is important.

As long as the child passes motion at least twice a week, the motion is not dry and hard and no difficulty/distress is involved in passing it, it is need not to be labeled as **constipation**.

Box 29.16 Causes of constipation in various age groups

- **Neonatal and infancy**
 - **Benign:** Insufficient intake of milk and fluids, artificial feeding, delayed introduction of semisolids and solids, prolonged use of laxatives and purgatives
 - **Organic:** Hirschsprung disease, congenital hypothyroidism, hypertrophic pyloric stenosis, duodenal atresia, meconium ileus, painful defecation as in anal fissure, intestinal parasitosis, CD, cystic fibrosis, anorectal malformations (anteriorly placed anus); spinal cord defects (tethered cord, meningocele)
- **Childhood:**
 - **Benign:** Poor dietetic intake, especially low residue diet, dependency on laxatives and purgatives, poor toilet training, unclean toilet, emotional problems
 - **Organic:** Intestinal parasitosis, anal fissure, intestinal obstruction (subacute), CD, CF
- **All age groups:**
 - **Drugs:** Anticholinergics, lead, opiates, phenobarbital, vincristine; abuse of laxatives
 - **Dietary:** Low residue diet.

Abbreviations: CD, celiac disease, CF, cystic fibrosis.

Etiology

Its causes are given in Box 29.16. Most children have functional constipation as a result of poor toilet training, low fiber diet with too much of liquid intake, drug abuse, etc. Only a small proportion have organic etiology such as congenital hypothyroidism, congenital megacolon (Hirschsprung disease), etc.

Congenital hypothyroidism and congenital megacolon are described in *See* Chapter 39 (Pediatric Endocrinology) and *See* Chapter 46 (Pediatric Surgery).

Diagnostic Evaluation

Clinical Work-up

A detailed history and physical examination is the gateway to arriving at the etiology of chronic constipation. Major aim is to determine whether the etiology is functional or organic. Box 29.17 lists the Rome III criteria for functional constipation. Points favoring organic etiology include:

- FTT
- Rectal bleed
- Vomiting
- Abdominal distention/pain
- Abdominal lump
- Enterocolitis manifesting as fever with recurrent diarrhea
- Spurious diarrhea
- Features suggestive of congenital hypothyroidism
- Recurrent respiratory infections.

Investigative Work-up

Investigations (other than routine), depending on the merit of a case, are usually required in only suspected organic constipation. These include:

- Rectal biopsy for congenital megacolon (Hirschsprung disease), hypoganglioneuroplasia and neuronal intestinal dysplasia
- Metabolic screening for CF, CD, lead poisoning, congenital hypothyroidism, etc

Box 29.17 Rome III criteria for functional constipation

Rome III diagnostic criteria for functional constipation in children upto 4 years of age

- Must include one month of at least two of the following:
 - Two or fewer defecations per week
 - At least one episode/week of incontinence after the acquisition of toileting skills
 - History of excessive stool retention
 - History of painful or hard bowel movements
 - Presence of a large fecal mass in the rectum
 - History of large diameter stools which may obstruct the toilet.

Rome III diagnostic criteria for functional constipation in children older than 4 years of age

- Must include two or more of the following:
 - Straining during at least 25% of defecations
 - Lumpy or hard stools in at least 25% of defecations
 - Sensation of incomplete evacuation for at least 25% of defecations
 - Sensation of anorectal obstruction/blockage for at least 25% of defecations
 - Manual manoeuvres to facilitate at least 25% of defecations (e.g. digital evacuation, support of the pelvic floor)
 - Fewer than three defecations per week
- Loose stools are rarely present without the use of laxatives
- Insufficient criteria for irritable bowel syndrome.

- MRI lumbosacral spine for spina bifida occulta and tethered cord
- Colonic transit study for pattern of colonic motility and delayed transit through anorectum.

Treatment

Treatment revolves around the correction of the underlying cause, dietary changes and behavioral training. In general, it needs to be ensured that child takes good deal of high residue diet and fluids and that the parents encourage him to use the toilet regularly.

- Role of drugs should be limited. The use of purgatives should be strongly discouraged. A mild laxative such as a glycerin rectal suppository or enema may be prescribed after careful consideration. However, make sure that the parents do not indulge in such medication frequently
- Ideally, the first line pharmacotherapy should be an osmotic laxative such as lactulose, 1–3 mL/kg/day or polyethylene glycol (PEG), 0.6–1 g/kg/day
- In order to safeguard against impaction, a stimulant laxative such as senna or bisacodyl may be used intermittently
- Prokinetics such as cisapride are not recommended
- Probiotics are of doubtful value
- Disimpaction is indicated in children with rectal impaction characterized by a large and hard fecalith (mass of feces) in the rectum. Its cleanout, using PEG is essential through a total bowel wash
- Finally, surgical causes need operative intervention.

VOMITING

Vomiting is usually nonspecific, but among the most frequently encountered symptoms in pediatric practice.

578 Definition

Vomiting is defined as forceful expulsion of contents of the stomach through the mouth. The strong contraction of the muscles of the abdominal wall is the triggering factor that operates in vomiting, irrespective of the cause. Vomiting is invariably preceded by nausea. Regurgitation is involuntary and effortless (not forcible) expulsion of small amounts of gastric contents. There is no preceding nausea in regurgitation.

Types

- **Short-lasting:** Most frequently occurring
- **Chronic/recurrent:** (1) Cyclic vomiting (greater than five stereotyped episodes), abdominal migraine, malrotation with volvulus; (2) Recurrent vomiting (greater than two episodes/week; one or emesis/hour)
- Persistent.

Etiology

As is evident from Box 29.18 a wide variety of conditions may be responsible for vomiting.

Clinical Features

The child first gets nausea which is followed by forcible expulsion of gastric contents via mouth. Depending on etiology, vomiting may be projectile and may contain bile or blood. There may be associated diarrhea or vertigo. Dehydration is likely to set unless fluid replenishment is instituted. Dangerous signs include:

- Presence of bile or blood in vomitus
- Severe abdominal pain/tenderness and distention
- Projectile vomiting
- Neck stiffness
- Photophobia
- Persistent tachycardia
- Hypotension
- Moderate-severe dehydration.

Box 29.18 Causes of vomiting in various age groups

- **Newborn:**
 - **Benign:** Swallowed air due to erratic feeding, possetting, swallowed amniotic fluid or blood
 - **Organic:** Septicemia or other infections, such as meningitis, intrauterine infections causing encephalitis, otitis, gastroenteritis; congenital obstructive defects of the GIT, birth trauma, birth defects of the CNS, hypoglycemia, galactosemia
- **Early infancy:**
 - **Benign:** Faulty feeding too much crying, loneliness
 - **Organic:** Infections such as meningitis, encephalitis, URI, whooping cough, gastroenteritis, congenital hypertrophic pyloric stenosis, hiatal hernia, pylorospasm, cow milk allergy, space-occupying lesions, diabetes, uremia, galactosemia.
- **Late infancy and childhood:**
 - **Benign:** Forcing the feed, as an attention-seeking device in upset parent-child relationship, motion sickness, cyclic vomiting.

Abbreviations: GIT, gastrointestinal tract; CNS, central nervous system; URI, upper respiratory infection.

Box 29.19 Important clues to etiology of vomiting

- **Vomiting:** Accompanied by diarrhea (concurrently or in due course); acute gastroenteritis
- **Bilious vomiting:** Lesion beyond ampulla of Vater
- **Nonbilious vomiting:** Lesion proximal to ampulla of Vater
- **Projectile vomiting:** Congenital pyloric stenosis, raised ICP
- **Stale food in the vomitus:** Gastric outlet obstruction
- **Visible peristalsis:** Obstruction
- **Early morning vomiting:** Brain tumor, cyclic vomiting syndrome
- **Vomiting with vertigo:** Middle ear disorder.

Abbreviation: ICP, intracranial pressure.

Diagnostic Evaluation

Clinical

A good history and clinical examination are important (Box 29.19). Assessment of hydration status is mandatory.

Investigative

- **Acute vomiting:**
 - Serum electrolytes
 - Blood creatinine
 - Plain X-ray of abdomen.
- **Chronic vomiting:**
 - **Blood chemistry:** Blood sugar, electrolytes, liver enzymes, serum amylase and lipase
 - **Imaging:** Abdominal ultrasonography, barium meal and follow through, cranial CT/MRI.

Complications

- Dehydration and dyselectrolytemia
- Constipation
- Malnutrition
- Esophageal injury—rupture (Boerhaave syndrome) or tear (Mallory-Weiss syndrome)

Treatment

Treatment is primarily of the cause, i.e. underlying condition. Every attempt should be made to arrive at the underlying cause through detailed history, clinical examination and, if need be, certain well-planned investigations. There is a rationale in symptomatically controlling persistent vomiting.

- An antiemetic such as ondansetron, domperidone, metoclopramide or promethazine
- Stomach wash
- Intravenous fluids.

RECURRENT APHTHOUS STOMATITIS

This the most common oral mucosal disease, is characterized by periodic painful single or multiple ulcers involving the buccal mucosa (Fig. 29.18).

Etiology

It remains elusive. Occurrence in families is well known, suggesting a strong hereditary component. Predisposing factors include poor orodental hygiene, nutritional



Fig. 29.18: Aphthous stomatitis. Note that the round and shallow ulcers are surrounded by inflammation.

deficiencies, food allergies, stress, hormonal changes, immunologic disorders, and HIV infection.

There is evidence that *Streptococcus* or *H. pylori* may be in its disease process.

Clinical Features

The round and shallow ulcers are surrounded by inflammation that mainly involves the nonkeratinized mucosa. These ulcers heal spontaneously in 1–2 weeks.

Diagnosis

Diagnosis is clinical.

Differential Diagnosis

Differential diagnosis is mainly from oral herpes simplex. Other conditions that should be considered include recurrent oral ulcers seen in CD, Crohn's disease, systemic lupus erythematosus (SLE) and Behcet's syndrome.

Treatment

It is empirical. For relief of pain and inflammation, topical medications (antimicrobial mouthwashes, topical steroids) are the mainstay. Other modalities include antibiotics and immune modulators.

THRUSH (ORAL MONILIASIS)

It is a common problem in newborns of mothers suffering from vaginal moniliasis, in the nurseries, in malnourished children and in patients on antibiotic therapy.

Clinical Features

Characteristically, the lesions are white elevated curd-like patches which cover lips, tongue, gums and the rest of the oral mucosa (Fig. 29.19). Extension into esophagus may cause esophagogastritis. This may result in feeding difficulties and aspiration into the lungs and pneumonia.



Fig. 29.19: Oral thrush (moniliasis). Note the white elevated curd-like patches. An attempt at removing them leaves behind an inflammatory area. This subject had been on prolonged treatment with antibiotics.

Diagnosis

It is purely clinical. Unlike curd patches, it is rather difficult to remove thrush with a tongue blade. The attempt leaves behind an inflammatory base.

Treatment

Response to local application of clotrimazole, nystatin 200,000 units/5 mL or 0.5% gentian violet is usually excellent.

GEOGRAPHICAL TONGUE

(Glossitis Areata Migrans)

This condition of unknown etiology is characterized by loss of papillae (other than fungiform ones) of the tongue resulting in erythematous areas which are sharply demarcated, irregular, smooth and often raised (Fig. 29.20).



Fig. 29.20: Geographical tongue. Note the sharply demarcated irregular and smooth areas. No treatment is indicated, excepting good orodental hygiene.

580 Typically, the lesions keep partially regressing or worsening but seldom disappear. At times, the child may complain of local irritation or burning sensation. No special therapy is indicated. Nonetheless, it is important to maintain good orodental hygiene to safeguard against superadded infection.

STRESS ULCER DISEASE

(Secondary Ulcer Disease)

Stress ulcers are defined as duodenal or gastric erosions or ulcers occurring as a complication of critical illnesses such as septicemia, hemorrhagic shock, burns, head injury, NSAIDs (aspirin, ibuprofen, nimesulide), steroids, antibiotics (chloramphenicol, penicillins, tetracyclines, cephalosporins), iron, calcium salts, potassium chloride or other severe physical trauma, etc. In the first 5 years of life, particularly in newborns, duodenal and gastric ulcers are usually of this nature.

Clinical Features

The condition usually manifests with acute massive painless bleeding on top of the signs and symptoms of the primary disease. Patients with predisposing conditions, but on measures that tend to reduce the gastric acidity (say, administration of ranitidine or antacids) are known to have far less incidence of stress ulcers and, if the latter at all occur, the severity is relatively within controllable limits.

Etiopathogenesis

Various pathologic factors include mucosal blood flow, mucus production and cell proliferation. All these factors interfere with host-defense mechanism.

Treatment

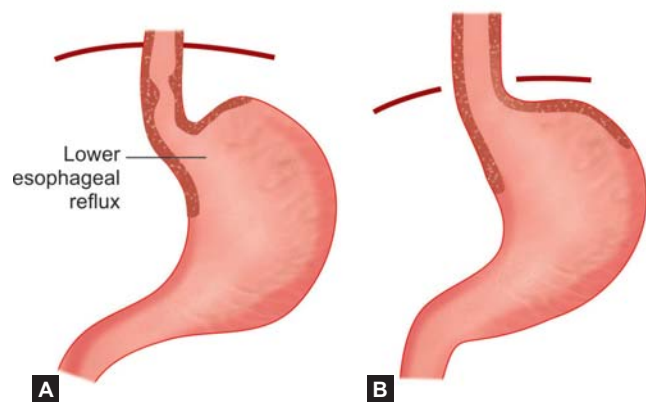
Therapy consists of giving large doses of antacids (to maintain gastric pH at or below 3.5) with or without histamine (H_2)-receptor blockers (ranitidine, cimetidine) to counter acidity. The latter is also for hastening the healing of the ulcers. The hydrogen pump inhibitors (omeprazole, lansoprazole) are excellent in treating erosions and ulcers secondary to NSAIDs.

Iced-saline lavage is excellent for stopping bleeding. Additional measures include blood transfusion, correction of coagulation defects and avoidance of acetylsalicylic acid. In the event of severe continuing bleeding, intra-arterial infusion of vasopressin (pitressin) or embolization therapy with gelfoam may be indicated. An occasional case may need suture ligation of the bleeding points together with vagotomy and pyloroplasty.

GASTROESOPHAGEAL REFLUX DISEASE

Definition

Gastroesophageal reflux disease (GERD) is defined as unprovoked passage of gastric contents (mostly acid/pepsin but sometimes even bilious constituents) into the esophagus due to incompetence of the esophageal



Figs 29.21A and B: Gastroesophageal reflux. Note the reduced length of intra-abdominal portion of the esophagus, poorly defined lower esophageal sphincter (LES) and obtuse angle of His in the second diagram. All the anatomical factors favor gastroesophageal reflux disease (GERD).

sphincter causing troublesome manifestations with or without complications (Figs 29.21A and B).

Risk Factors

Box 29.20 lists the risk factors that predispose to GERD.

Clinical Features

- Excessive and regurgitation, vomiting and rumination
- Dysphagia
- Hematemesis
- Cough, wheezing, stridor, hoarseness
- Chest pain /heart burn
- Failure to thrive—poor weight gain or even weight loss
- Sandifer syndrome—spasmodic torsional dystonia, opisthotonos, arching of back.

Complications

- Aspiration pneumonia, especially in infancy
- Recurrent pneumonia
- Chronic cough
- Wheezing.

Diagnosis

- History and physical examination are important in suspecting GERD.
- **Barium esophagogram:** Barium swallow done under fluoroscopy nearly confirms the diagnosis. Presence of a stricture or an associated hiatal hernia (seen as

Box 29.20 Risk factors predisposing to GERD

- Obesity
- Prematurity
- CP
- Hiatal hernia
- Cystic fibrosis
- Esophageal atresia (repaired)
- Persistent regurgitation (spilling) beyond 3 months of age
- Family history of GERD.

Abbreviations: GERD, gastroesophageal reflux disease; CP, cerebral palsy.

longitudinal gastric folds above the diaphragm) may also be detected at the same time

- **Esophageal 24 hours pH monitoring:** In cases strongly suspected of GERD, but not corroborated by barium esophagogram, repeated studies or prolonged esophageal 24 hours pH monitoring may prove of value. It detects only acid reflux episodes
- **Combined 24 hour multiple intraluminal impedance and pH monitoring:** It has an edge over plain pH monitoring since it also detects nonacid reflux episodes
- Upper GI endoscopy
- Endoscopic biopsy
- Technetium scintiscan is another valuable diagnostic tool
- **Empirical trial of acid suppression:** It is useful in older children and adolescents presenting with such symptoms as heart burn/chest pain in whom a 4-week trial with a proton pump inhibitor (PPI) may be justified.

Differential Diagnosis

An important differential diagnosis is the so-called **eosinophilic esophagitis**, usually secondary to food or environmental allergy. This newly recognized entity should be considered in relapsing or refractory cases of GERD.

Management

Conservative Measures

Most infants with GER respond to careful attention to burping and propping upright during and for one hour after feeding. In those who fail to respond, positional therapy should be extended for 24 hours a day. Recently, it has been advocated that a 30° prone position with a slight right lateral tilt is far better than the supine upright position or an infant seat with 30–60° reclining. Additional measures include administration of thickened feeds.

Pharmacotherapy

- Proton pump inhibitor such as omeprazole, lansaprazole and esomeprazole (Box 29.21) are the drugs of choice.
- Drugs that may be used in some cases:
 - Antacids or ranitidine for esophagitis
 - Prokinetics like domperidone or metoclopramide to accelerate gastric emptying and stimulate muscular activity in the esophagus, and cisapride to

enhance gastrointestinal contraction, anteroduo-
denal coordination and lower esophageal sphincter (LES) pressure.

Accelerated weight gain and reduction in vomiting are the earlier signs of favorable response.

Surgery

Indications for surgery are

- Failure to respond to a 6 week course of intensive medical treatment
- Presence of a stricture
- Recurrent aspirations and apnea.

Antireflux surgery, fundoplication, is of value in decreasing chronic relapsing GERD in a proportion of children. However, risk of postoperative morbidity and failure is high in subjects with very severe GERD.

Prognosis

Nearly all infants become symptomatic by 6 weeks of age though in most symptoms are present right in the first week. By 2 years of age, 60% of the patients become asymptomatic. In the rest, symptoms continue till the age of 4 years or even more.

DYSPHAGIA

Definition

Dysphagia (difficulty in swallowing) is defined as a sensation of hindrance of passage of food from mouth to stomach. It may be oropharyngeal or esophageal.

- Odophagia is defined as painful swallowing
- Globus is defined as a sensation of a lump in throat.

Etiology

Box 29.22 lists important conditions causing dysphagia.

GASTROINTESTINAL BLEEDING

(Gastrointestinal Hemorrhage)

Gastrointestinal hemorrhage, a common childhood problem, may be from upper GIT or from lower gastrointestinal tract with ligament of Treitz as the landmark.

Understandably, it may present as **hematemesis** or coffee-ground-colored emesis, or blood per rectum which may be fresh (**hematochezia**) or chemically altered, i.e. dark/black in color (**melena**). Certain definitions in relation to GI bleed are given in Box 29.23.

Box 29.21 Recommended PPI in GER

- Omeprazole, 0.7–3.3 mg/kg/day (maximum 80 mg/day)
- Lansaprazole, 0.6–1.6 mg/kg/day (maximum 60 mg/day)
- Esomeprazole, 0.5 mg/kg/day
- Pantaprazole, 0.4–0.8 mg/kg/day
- Rabeprazole, 0.2–0.4 mg/kg/day

Abbreviations: PPI, proton pump inhibitor; GER, gastroesophageal reflux.

Box 29.22 Important conditions causing dysphagia

- Strictures
 - Congenital stricture
 - Corrosive stricture
 - Post TEF repair stricture
 - Post-sclerotherapy stricture
 - Peptic stricture
- Infectious esophagitis
- Foreign body in esophagus
- Achalasia cardia
- Eosinophilic esophagitis.

Abbreviation: TEF, tracheoesophageal fistula.

Box 29.23 Certain definitions related to GI bleeding

- **Upper GI bleed:** Bleeding from a site proximal to ligament of Treitz*
- **Lower GI bleed:** Bleeding from a site distal to the ligament of Treitz
- **Hematemesis:** Blood-stained or frankly bloody vomitus which is bright red or coffee-ground in color depending on the severity of the bleed and duration of contact with gastric secretions. It suggests an upper GI bleed, usually esophageal varices. Other causes include severe gastritis, bleeding or coagulation disorder
- **Melena:** Altered (denatured) blood in stools giving it a black-tarry look. It suggests upper GI bleed or bleed from small intestine proximal to distal ileum, e.g. hookworm infestation
- **Hematochezia:** Bright red blood in stools suggestive of rectal/colonic bleed, e.g. hemorrhoids, polyp, anal fissure or fistula
- **Dysentery:** Bloody diarrhea, usually infective in origin (*Shigella*).

* *Ligament of Treitz:* A muscular band that functions like a ligament at the level of the duodenojejunal flexure.

Abbreviation: GI, gastrointestinal.

Etiology

It depends on the age of the patient, on bleeding whether it is from upper or lower GIT, on magnitude of bleeding, on associated symptoms and signs, and on general condition of the patient.

Upper Gastrointestinal Bleeding

- **Newborn period:** Swallowed maternal blood, hemorrhagic disease of the newborn, sepsis, necrotizing enterocolitis, stress ulcer of stomach or duodenum, trauma from nasogastric tube, hemorrhagic gastritis, hiatal hernia, esophageal or duodenal atresia, foreign body impaction, vascular malformations and idiopathic
- **Infancy and childhood:** Swallowed blood after epistaxis, tonsillectomy, bleeding from gums, esophageal varices, portal hypertension, peptic ulcer, erosive gastritis/esophagitis, reflux esophagitis, sharp foreign body, gastric outlet obstruction (pyloric stenosis), HSP, hemangioma, telangiectasia, tumor, blood dyscrasia.

Lower Gastrointestinal Tract Bleeding

- **Newborn period:** Swallowed maternal blood, hemorrhagic disease of the newborn, necrotizing enterocolitis, anal or rectal fissure/ulceration, GIT infection with organisms such as *Escherichia coli*
- **Infancy and childhood:** Anal fissure, swallowed blood (from epistaxis, tonsillectomy or dental extraction), varices, stress ulcer, peptic ulcer, NSAID-induced gastric ulcer, polyps, intussusception, dysentery, ulcerative colitis, Crohn's disease, intestinal parasites, Meckel diverticulum, duplication of the gut, HSP, hemolytic uremic syndrome, hemangioma, telangiectasia, cow milk protein allergy, hemorrhoids.

Diagnosis

In doubtful cases of GIT bleeding, it must be confirmed if it is really blood and coming from the GIT. Ingestion of iron or bismuth-containing preparations or eating earth or charcoal (pica) may simulate melena. It is a good practice to confirm the presence of blood chemically.

History and Physical Examination

Find the amount of blood loss, any previous history of bleeding, any constipation or diarrhea, abdominal or joint pain, epistaxis, surgery on tonsils, etc.

Is the child acutely sick? Is he in shock due to excessive blood loss? How are the vital signs?

Always look for evidence of portal hypertension, hemangioma, purpura, telangiectasia, intestinal obstruction and blood dyscrasia. Painless passage of a large amount of blood invariably points to esophageal varices. Always find out other evidence of portal hypertension such as splenomegaly, superficial abdominal venous network and ascites. Nasal passages should be carefully inspected for signs of epistaxis and anus and rectum for fissure, polyps and hemorrhoids.

Investigations

- A complete blood count, bleeding time (BT), coagulation time (CT), prothrombin time (PT), platelet count, blood group and cross-matching
- Passage of nasogastric tube into the stomach may reveal if the source of blood is upper GIT. Presence of blood in the gastric aspirate confirms that the bleeding site is proximal to the ligament of Treitz
- Barium swallow
- Barium enema is indicated in case of the lower GIT bleeding. Remember to thoroughly clean the bowel in suspected polyp. In intussusception or malrotation with volvulus, such cleaning is contraindicated
- Sigmoidoscopy is necessary in the presence of evidence favoring polyps or colitis
- Diagnostic laparotomy in cases of significant bleeding in whom diagnosis has defied all the investigations.

Management**Upper Gastrointestinal Bleeding**

Management is mainly of the etiologic condition and the blood loss.

- **Supportive measures:** Massive bleeding, causing shock, irrespective of the etiology, is an indication for intravenous fluids and blood transfusion. Box 29.24 lists the stepwise stabilizing approach
- **Specific measures:** In upper GI bleeding from mucosal erosion or ulceration, repeated irrigation with tap water

Box 29.24**Stepwise stabilizing approach in gross GI bleed**

- IV line establishment for appropriate venous access
- Blood for grouping, cross-matching and other investigations
- Oxygen in case of loss of one-fifth blood volume
- Central venous line for maintaining pressure at 3–8 cm of water
- IV infusion of bolus normal saline or Ringer lactate 10–20 mL/kg speedily
- Whole blood or packed cell transfusion to raise hemoglobin to a minimum of 8 g/dL
- Monitor hematocrit (target at 30%) and urine output
- Short-term antibiotic prophylaxis.

Abbreviation: IV, intravenous; GI, gastrointestinal.

or saline plus neutralization or prevention of release of gastric acid through medication (antacid, H_2 receptor antagonists like ranitidine, omeprazole, sucralfate) usually control it. Management of persistent bleed from esophageal varices comprises:

- Administration of somatostatin or octeotide
- Endoscopic sclerotherapy/endoscopic variceal ligation
- Endoscopic injection of tissue adhesive glue in gastric varices
- Temponade of varices
- Transjugular intrahepatic portosystemic shunt (TIPS). Surgical intervention is indicated in such situations as:
- Intussusception
- Volvulus
- Meckel diverticulum or tumors
- Ongoing bleeding despite conservative measures in peptic ulcer or stress ulcer disease.

Lower Gastrointestinal Bleeding

- Supportive measures are virtually on the same lines as for upper GI bleed
- Specific measures are dictated by the etiologic condition.

Prognosis

The unfavorable prognostic factors include:

- Massive hematemesis
- Initial hematocrit of 20%
- Severe anemia with Hb under 7 g/dL
- Infusion of over 85 mL/kg of blood
- Undetected source of bleed, frank blood or clots in upper GIT
- Coexisting liver disease or other systemic disorder
- Coagulation abnormality.

HELICOBACTER PYLORI INFECTIONS

This spiral-shaped Gram-negative bacteria with unipolar flagella was first discovered in 1983 by Barry Marshall and Robin Warren and initially christened *Campylobacter pyloridis*. Its characteristics include ability to produce abundant urease and unique fatty acid composition.

Epidemiology

Helicobacter pylori infection is truly an infection of children in most of whom it lasts throughout their life. The development of stomach and duodenal disease depends on certain risk factors which remain to be precisely defined. The incidence is very high in underprivileged communities. Feco-oral route appears to be the major route of acquiring infection with clustering in families and within institutions for mentally retarded and orphanages.

Pathogenesis

The organism is highly host and tissue specific, invading predominantly the mucos layer overlying the gastric epithelium in the antrum and causing gastric inflammation and epithelial changes. The modus operandi of production

of inflammation is explained by two hypothesis, termed **leaking roof hypothesis** by Goodwin and **gastrin-link hypothesis**.

Clinical Features

Most children with *H. pylori* infection are asymptomatic. In a proportion of cases, chronic gastritis may manifest with recurrent abdominal pain and vomiting. There is a strong evidence of an association between *H. pylori* infection and gastritis (antral) as well as duodenal ulcer disease. Remaining manifestations include refractory IDA, protein losing enteropathy and malabsorption.

Diagnosis

Noninvasive investigations include urea breath test (UBT), preferably employing [13c]-urea (rather than [14c]-urea) which can be toxic to children because of radioactivity and serology. Invasive investigations include flexible upper gastrointestinal endoscopy to biopsy the gastric mucosa for histopathology, culture or rapid urease test.

Differential Diagnosis

Gastrospirillum hominis, an organism resembling *H. pylori*, though longer than it, also causes chronic gastritis. It is corkscrew-shaped and is found at neck of pyloric glands in gastric pits.

Treatment

Since *H. pylori* infection is likely to be present at an early age (say 3 months), the target for intervention is probably early infancy.

Unlike in adults where **triple therapy** (chosen out of bismuth salt, amoxicillin/ampicillin/tetracycline, metronidazole/tinidazole, omeprazole/ranitidine, clarithromycin) is known to give best results, dual therapy is preferred in children. Best results (100%) are obtained employing a combination of amoxicillin and bismuth subsalicylate. A combination of amoxicillin and tinidazole too gives very good results (94%). In view of the likelihood of salicylism through use of bismuth subsalicylate in children under 10 years, this agent should be avoided in this age group. Instead, colloidal bismuth subcitrate may be used. The known toxicity of bismuth (encephalopathy, ARF) in adults is rare in childhood. If **dual therapy** fails, pediatric *H. pylori* infection may be treated with **triple therapy**. Some experts do not favor routine pharmacotherapy for *H. pylori* infection in children.

FOOD ALLERGY

The term denotes a group of disorders [both immunoglobulin E (IgE) and non-IgE-mediated] in which manifestations follow immunologic responses to specific food antigens. The incidence is around 6% in first 3 years of life.

Causative Foods

The most common cause of food allergy in early infancy is cow milk or soy protein allergy followed by allergy to

584 peanut or egg (white) either through the mother's diet or through direct feeding. In later infancy, and childhood, wheat emerges as the most important food allergy.

Common offending coloring additives used in foods and additives are tartrazine, sunset yellow, carmoisine and amaranth. These additives may cause hyperactive behavior over and above atopy.

Operational Mechanisms

The possible mechanisms of such adverse reactions to foods include:

- Immunologic IgE-mediated either toxic complex (alpha-gliadin) or cell (lymphocyte)-mediated injury
- Biochemical enzyme deficiency (lactase, etc.), nitrite sensitivity (hog dog headache), tyramine headache, toxic effect (alpha-gliadin)
- Reaction to color and flavoring additives.

A number of adverse reactions to whole cow milk ingestion may occur, e.g.:

- Occult fecal blood loss with resultant anemia
- Enteropathy with loss of protein and blood
- Vomiting and diarrhea
- Heiner syndrome characterized by pulmonary hemosiderosis, chronic rhinitis, recurrent otitis media, GI symptoms and growth failure
- Recurrent pulmonary infiltrates in X-ray
- Multiple precipitating antibodies
- Disaccharide intolerance.

Clinical Features

- **IgE-mediated food allergy** causing rapid development of symptoms may manifest in the form of GIT symptoms (itching, tingling or angioedema of lips, tongue, throat and palate, vomiting, diarrhea, crampy abdominal pain) or non-GIT symptoms (rhinitis, conjunctivitis, urticaria, angioedema, atopic dermatitis, asthma, anaphylaxis, etc.).
- **Non-IgE-mediated food allergy** causing symptoms over hours to days, manifests as allergic proctocolitis, enterocolitis, enteropathy, allergic eosinophilic, gastroenteritis and dermatitis herpetiformis associated with CD and pulmonary hemosiderosis (Heiner disease).
- **Combined IgE-mediated and non-IgE-mediated reactions** can too occur.
- Association between food allergy and behavioral manifestations remains speculative and needs further elucidation.

Diagnosis

Diagnosis is usually by critical testing of the offending food by elimination and provocation (challenge) method, the so-called **double-blind placebo-controlled food challenge** (DBPCFC) which is the gold-standard. Emotional bias of the parents and the child must not be allowed to operate while conducting the tests.

Skin and radioallergosorbent test (RAST) assay may be employed to identify presence of IgE antibody to food.

Provocative/neutralizing methods of diagnosing allergy by intradermal injection or sublingual administration should no longer be encouraged. The so-called **eosinophilic gastroenteritis** is diagnosed by demonstrating the number of eosinophils in small intestinal or gastric biopsy.

Treatment

For an acute severe life-threatening IgE-mediated reaction, injectable epinephrine and/or hydrocortisone may be needed.

Treatment is directed at elimination of the offending food. With passage of time, it becomes possible to cautiously reintroduce the offending food into the diet as such or under cover of cromolyn sodium 60–200 mg [O (oral)] 30 minutes before giving the food.

BEZOARS

The term denotes a group of conditions in which there is a collection of exogenous matter in the stomach or intestine.

The incidence is highest in females in second decade of life, especially with disturbed personality. Accumulation of hair is referred to as **trichobezoars**, plants and animal material as **phytobezoars**, calcium or casein content as **lactobezoars**.

Manifestations are of gastric outlet or partial intestinal obstruction, severe halitosis, secondary IDA, hypoproteinemia and steatorrhea.

ABDOMINAL TUBERCULOSIS

Involvement of abdomen in tuberculosis may be in the following forms:

- **Peritoneal:** Ascitic (wet) or plastic (dry)
- **Intestinal:** Ulcerative, hypertrophic or ulcerohypertrophic
- **Glandular:** Mesenteric lymph nodes
- **Viscera:** Solid viscera such as liver.

Clinical Features

Manifestations include:

- Unexplained fever, malaise, easy fatigability, anorexia
- Chronic/recurrent diarrhea, abdominal discomfort/pain, abdominal distention, weight loss
- Ascites out of proportion to edema elsewhere
- Lump(s)—lymph nodes, ileocecal mass, loculated ascites.

Diagnosis

Abdominal tuberculosis is among the tough diagnostic problems. High index of suspicion is a real forerunner for arriving at the diagnosis which needs to be established through investigations.

- **Ascitic fluid:** In tuberculous abdomen, it is an exudate with predominance of lymphocytes, low serum: ascitic fluid gradient and high adenosine deaminase.
- **Imaging:** CT abdomen is best in detecting enlarged lymph nodes. Chest X-ray may show evidence of a pulmonary lesion.

- Fine needle aspiration cytology (FNAC), lymph node biopsy, liver biopsy for demonstration of acid-fast bacilli (AFB) and pathological changes of tuberculous granuloma with caseation.
- Polymerase chain reaction (PCR).

Treatment

Notwithstanding investigative work-up turning out to be of limited help, empirical antituberculosis treatment (ATT) is justified in the wake of strongly suggestive clinical scenario, including exclusion of differentials such as inflammatory bowel disease (Crohn's disease in particular), lymphoma, etc.

ATT comprising of four drugs isoniazid (INH), rifampicin, pyrazinamide and ethambutol \times 2 months. Then, pyrazinamide is withdrawn and other three continued for remaining 4 months. In view of ethambutol rarely causing optic atrophy, a periodic ophthalmic checkup is strongly recommended.

During the course of ATT, child must be observed for ATT-induced hepatitis. Indications of surgical intervention are:

- Intestinal obstruction
- Perforation
- Severe hemorrhage.

INTESTINAL FAILURE

Definition

By definition, intestinal failure is a grossly inadequate intestinal function with severe malabsorption as a result of a disease in which the patient becomes dependent on TPN for his survival.

Etiology

Though a number of conditions may cause intestinal failure (Box 29.25), the most frequently cause is short bowel syndrome.

Complications

- TPN-related liver disease
- Catheter-associated sepsis

Treatment

Depending on the merit of the case, treatment of choice is

- Intestinal transplantation as such, or
- Intestinal transplantation plus liver transplantation in the presence of TPN-related liver disease.

SURGICAL GASTROINTESTINAL PROBLEMS

These are detailed in Chapter 46 (Pediatric Surgery).

Box 29.25 Etiology of intestinal failure

- **Short bowel syndrome**
 - Necrotizing enterocolitis
 - Volvulus (midgut)
 - Gastroschisis
 - Gut trauma
- **Dysmotility syndrome**
 - Neuropathies
 - Myopathies
- **Mucosal enteropathy**
 - Autoimmune enteropathy
 - Microvillous inclusion disease
 - Tufting enteropathy.

Multiple Choice Questions

- Spot the incorrect observation:
 - The 24 hour pH monitoring is no longer considered a gold standard for diagnosis of gastroesophageal reflux disease
 - Ligament of Treitz is not a true ligament, but a band of muscle fibers
 - The term, recurrent abdominal pain, is now replaced with chronic abdominal pain
 - Ampicillin is an important cause of antibiotic associated diarrhea which may take the shape of pseudomembranous colitis
 - Osmolarity of low osmolarity ORS is 245 mOsm
- All of the following observations about diarrhea are correct, except:
 - Rotavirus diarrhea, the most common form, is preventable via rotavirus vaccine
 - Persistent diarrhea, invariably follows acute infective diarrhea lingering on for 14 days or more
 - Chronic diarrhea has the same cut off point of 2 weeks but diarrhea is usually secondary to significant malabsorption
 - Antimotility drugs are safe in acute diarrhea in children
 - Celiac disease may be complicated by leukemia or lymphoma for months and even years following the diagnosis
- Which one is not a feature of acrodermatitis enteropathica:
 - Cutaneous lesions
 - Crazy pavement dermatosis
 - Diarrhea
 - Alopecia
 - Atrophic nails

contd...

4. Patchy lesions (the so-called "skip lesions") are an important feature of:
 - A. Ulcerative colitis
 - B. Crohn's disease
 - C. Indeterminate inflammatory bowel disease
 - D. Celiac disease
 - E. Tropical sprue
5. Each of the following statements is incorrect, except:
 - A. Protein energy malnutrition, even when it is severe, seldom cause villous atrophy
 - B. The most common cause of food allergy in early infancy is cow milk protein (CMP) allergy
 - C. Most children with *H. pylori* infection are symptomatic
 - D. Gastrointestinal hemorrhage, regardless of its magnitude and location, is an indication for blood transfusion
 - E. Monosaccharide malabsorption is very common in children

Answers

1. A 2. D 3. B 4. B 5. B

Clinical Problem-solving**Review 1**

A 2-year-old child, a known case of Hirschsprung disease awaiting surgery, has been treated for severe pharyngitis with oral ampicillin. Five days after stopping treatment, he develops abdominal cramps with bloody diarrhea and fever.

1. What is the most likely cause of child's abdominal manifestations and why?
2. How to confirm this diagnosis?
3. What is its precise treatment?

Review 2

A 7-month-old bottlefed infant, weighing 4.5 kg, is referred by a practitioner for acute diarrhea and vomiting with severe dehydration. Despite IV drip employing Darrow's solution for one hour at the practitioner's clinic, the infant's condition has worsened.

1. Was the practitioner's selection of IV fluid appropriate?
2. What is the initial recommended fluid therapy in severe diarrheal dehydration?
3. Does this child need antibiotic?

Answers**Review 1**

1. In view of two apparent predisposing factors, namely Hirschsprung disease and ampicillin therapy, this appears to be a case of pseudomembranous colitis resulting from toxins A and B of toxigenic strains of *Clostridium difficile*.
2. For establishing the diagnosis, we need to detect the causative bacteria, *Clostridium difficile*, in culture and toxin A by ELISA or latex agglutination assay and toxin B by cytotoxicity to fibroblasts.
3. Therapy revolves around metronidazole, vancomycin or sometimes both.

Review 2

1. No, Darrow solution which has high potassium is not appropriate for initial rehydration in severe diarrheal dehydration. WHO recommends Ringer lactate as the initial IV fluid in severe diarrheal dehydration.
2. The infant under review needs 30 mL/kg within first hour followed by 70 mL/kg over next 5 hours.
3. Antibiotic therapy is usually not indicated in acute diarrhea. However, underlying severe malnutrition, especially in the presence of fever, in this infant warrants administration of a suitable antibiotic.

FURTHER READING

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BASICS OF HEPATOBILIARY SYSTEM

Liver, the largest organ of the body, along with gallbladder and bile ducts, develops from an evagination of the foregut into the mesoderm of septum transversus.

The biliary system consists of biliary canaliculi (which join to form bile ductules), bile ducts and hepatic ducts (which join to form common bile duct at the portahepatis). The common bile duct along with the main pancreatic duct opens at the ampulla of Vater in the duodenum (Fig. 30.1). Blood supply is 75% from portal vein and 25% from hepatic artery. Venous drainage is by hepatic veins that drain directly into the inferior vena cava. Hepatic lobules form the basic architecture. In between the liver cells (hepatocytes) and sinusoids are spaces containing tissue fluid.

FUNCTIONS OF LIVER

- Synthesis of most of the plasma proteins (albumin, globulin, fibrinogen), transport proteins, coagulation factors (fibrinogen, prothrombin, clotting factors V, VII, IX, X, XIII) and components of the complement system
- Elimination of nitrogenous waste by amino acid degradation

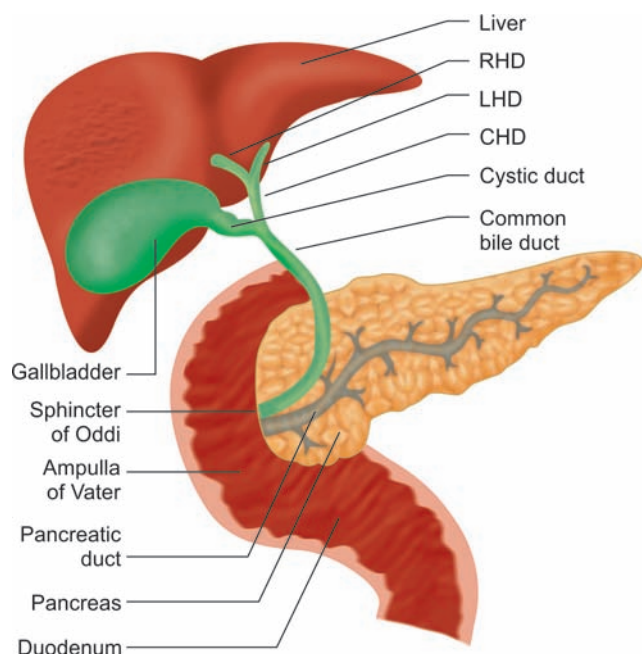


Fig. 30.1: Hepatobiliary system. A diagrammatic representation.

Note: RHD, right hepatic duct, LHD, left hepatic duct, CHD, common hepatic duct.

- Regulation of blood glucose levels by glycolysis and gluconeogenesis
- Desaturation of fats
- Fat digestion by bile
- Storage of vitamins A, D, E, K, B12, iron and copper
- Detoxification of drugs, including alcohol
- Inactivation of hormones.

MANIFESTATIONS OF LIVER DISEASE

- **Common symptoms**
 - Icterus (jaundice)
 - Pruritus
 - Abdominal pain/distention
 - Clay-colored stools
 - Dark-colored urine
 - Fluid retention
 - Nonspecific symptoms in the form of nausea, vomiting and malaise
 - Neuropsychiatric symptoms such as change in sensorium, confusion and altered sleep rhythm.
- **Common signs**
 - Icterus
 - Hepatomegaly with or without splenomegaly
 - Spider angiomas
 - Palmar erythema
 - Xanthomas
 - Caput medusae
 - Ascites
 - Flapping tremors
 - Portal hypertension.
- **Additional manifestations**
 - Endocrinal abnormalities
 - Renal dysfunction (hepatorenal syndrome).

HEPATIC MANIFESTATIONS OF SYSTEMIC DISEASES

Box 30.1 lists the hepatic manifestations of systemic diseases.

DIAGNOSTIC WORK-UP FOR SUSPECTED LIVER DISORDER

Clinical Evaluation

As emphasized in Chapter 2 (Pediatric History-taking and Physical (Clinical) Examination), a good history and physical examination together with skillful interpretation of the common symptoms and signs lay the foundation stone for deciding on the various investigations to arrive at the final diagnosis in a suspected child with liver disease.

Box 30.1 Hepatic manifestations of systemic diseases**GIT disorders**

Celiac disease—raised liver enzymes (transaminases)

Endocrinal disorders

- **Diabetes mellitus:** Fatty liver
- **Congenital hypothyroidism:** Prolonged neonatal jaundice beyond first month of life.

Hematological disorders

- **Thalassemia major:** Chronic iron overload (hemosiderosis/fibrosis, cirrhosis, superadded hepatitis B and C from contaminated blood transfusion)
- **Sickle-cell anemia:** Acute hepatic crisis, superadded hepatitis B and C from contaminated blood transfusion and cholecystitis (both acute and chronic) from pigment stones.

Immunological disorders

SLE: Hepatomegaly, autoimmune hepatitis, transient cholestasis in neonatal SLE.

Fulminant infections

- **Neonatal sepsis:** Icterus and hepatocellular necrosis from pneumococcal infections; hemolysis from *Clostridium difficile* infection
- **Enteric fever:** Elevated alkaline phosphatase, aminases, lactate dehydrogenase and hepatitis
- **Dengue hemorrhagic fever:** Poor liver function with elevated transaminases
- **Malaria:** Poor liver function with elevated transaminases.

Cardiac disorders

- **Acute heart failure:** Tender hepatomegaly
- **Chronic heart failure:** Hepatomegaly and cardiac cirrhosis
- **Cardiac surgery:** Shock, hypoperfusion
- **Alagille syndrome:** Cholestasis.

Ischemic disorders

- **Shock:** Hypoperfusion of liver, coagulopathy
- **Encephalopathy:** Icterus.

Bone marrow transplantation

- **Chemotherapy (conditioning):** VOD
- **GVHD:** Liver dysfunction
- **Sepsis:** Liver dysfunction
- **Toxins:** Liver dysfunction.

Oncologic diseases

- **Leukemia:** Icterus from hepatic infiltration
- **Lymphoma:** Icterus from hepatic infiltration.

Abbreviations: SLE, systemic lupus erythematosus; VOD, veno-occlusive disease; GVHD, graft versus host disease; GIT, gastrointestinal tract.

Investigative Evaluation

Aims of various investigations are:

- Is the child indeed suffering from a liver disorder?
- If he is, then what is the precise diagnosis?
- How severe is it?
- What is the specific treatment and prognosis?
- **Biochemical tests (liver function tests)** include serum bilirubin with conjugated and unconjugated fractions, aminotransferase levels, alkaline phosphatase, prothrombin time and albumin.
- Serum bilirubin and its fractions assist in distinguishing between hemolysis and hepatic dysfunction. A significantly high conjugated fraction is a sensitive index of hepatocellular disease or hepatic excretory dysfunction.
- Aminotransferase levels are very sensitive indices of hepatocellular damage. Whereas alanine transaminase

(ALT) is liver specific, aspartate aminotransferase (AST) is also derived from other organs. **589**

- Serum prothrombin and albumin levels are reflective of hepatic synthetic function.
- **Percutaneous liver biopsy** detailed later in Chapter 49 (Pediatric Practical Procedures) is of considerable help in—Providing exact histologic diagnosis in diseases such as Indian childhood cirrhosis (ICC), neonatal cholestasis, chronic active hepatitis, Reye syndrome, intrahepatic cholestasis, congenital hepatic fibrosis or undefined portal hypertension.
- Enzyme analysis in inborn errors of metabolism.
- Analysis of stored material such as iron, copper or specific metabolites.
- **Hepatic imaging procedures** include a plain X-ray of abdomen, barium swallow, ultrasonography, computed tomography (CT) scan, magnetic resonance imaging (MRI), radionuclide scanning, cholangiography, endoscopic retrograde cholangiopancreatography (ERCP) and selective angiography.

ACUTE VIRAL HEPATITIS

Today, viral hepatitis (primary) is considered to be caused by at least five specific viruses:

1. Hepatitis A virus (HAV)
2. Hepatitis B virus (HBV)
3. Hepatitis C virus (HCV) (new name for post-transfusion non-A, non-B virus)
4. Hepatitis D virus (HDV)
5. Hepatitis E virus (HEV) (new name for eternal non-A, non-B virus)
6. Newer hepatitis viruses, whose exact role in human disease is yet to be fully ascertained, are:
 - Hepatitis F virus
 - Hepatitis G virus
 - GB agent (GB virus A, GB virus B)

In addition, a number of other viruses (cytomegalovirus {CMV}, Epstein-Barr virus {EBV}, herpes simplex virus {HSV}), bacterial infection (syphilis, leptospirosis, septicemia), drugs (isoniazid {INH}, erythromycin estolate, paracetamol, chlorpromazine) and diseases (alpha-1-antitrypsin deficiency, Wilson disease, galactosemia, congenital cardiac failure {CCF}, veno-occlusive disease {VOD}, anoxia, shock, infarction) produce a hepatitis-like syndrome.

Etiologic Viruses

- **Hepatitis A virus** is a ribonucleic acid (RNA) virus which is very much identical to enteroviruses. It measures 27 nm and produces raised titer of anti-HAV immunoglobulin (IgM) antibody in the serum which is important for its serologic diagnosis as also anti-HAV IgG antibody which persists virtually forever, thereby preventing reinfection. Chronic infection never occurs.
- **Hepatitis B virus** (Dane particle) is a deoxyribonucleic acid (DNA) virus, measuring 42 nm with complex structure consisting of hepatitis B surface antigen (HBsAg), a central or core antigen (HBcAg) and DNA polymerase. Another antigen, HBhAg, appears to be a

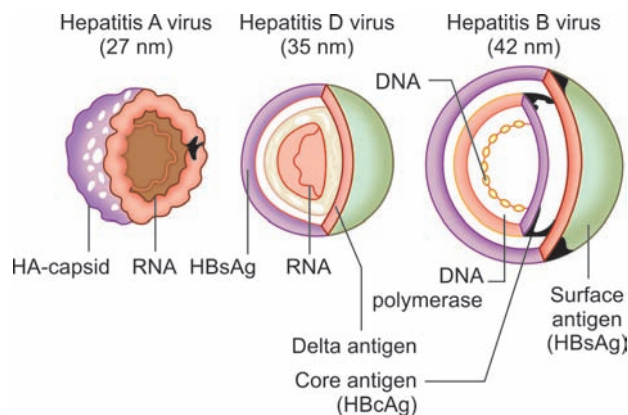


Fig. 30.2: Hepatitis viruses: Diagrammatic representation of structures of hepatitis A, B and D viruses.

part of HBcAg. Its presence in serum points to highly contagious stage; presence beyond 6 months to a chronic infection.

- **Hepatitis C virus** is an RNA virus, measuring 60–70 nm. It was formerly designated post-transfusion non-A, non-B hepatitis virus. Its serum marker is anti-HCV (IgG, IgM).
- **Delta virus** (HDV) is an RNA virus, measuring 36 nm, which is associated with a nucleoprotein (delta antigen) and covered with HBsAg. It needs HBsAg for its replication and expression. The presence and spread of HDV is, therefore, closely linked with HBsAg.
- **Hepatitis E virus** is an RNA virus, measuring 32–34 nm. It was formerly designated as eternal non-A, non-B hepatitis virus. Its serum marker is anti-HEV. Figure 30.2 provides diagrammatic representation of HAV, HBV and HDV.

Mode of Infectivity

- **Hepatitis A:** Gastrointestinal tract (GIT) is the possible portal of entry. Occasionally, HAV can gain entry via blood as well. During the early stages of the disease, virus can be isolated in the blood as well as stools. It continues to pass in stools as long as complete recovery does not occur.
- **Hepatitis B:** Transmission is almost always via the inapparent parenteral route, e.g. blood transfusion, injection, vaccination, skin or mucosal abrasion, etc. Transplacental passage may affect the fetus causing neonatal hepatitis. Nonetheless, child to child infection, occurring during plays or bed-sharing via skin lesions like impetigo, scabies, cuts and infected insect bites is the major cause of hepatitis in childhood.
- **Hepatitis C:** Mode of transmission is parenteral, transfusion or vertical (sexual).
- **Hepatitis D:** Transmission is virtually on the same lines as in serum hepatitis. However, vertical transmission from mother to the infant is infrequent.
- **Hepatitis E:** Mode of transmission is enteral, usually water-borne.

Clinical Features

- **Incubation period** of hepatitis A varies from 28–42 days. In case of hepatitis B, it is much longer, i.e. 60–150 days.



Fig. 30.3: Acute viral hepatitis. Note the icterus which followed a couple of days after nausea, vomiting, abdominal discomfort, malaise and anorexia. Liver was palpable 3 cm below the costal margin with a span of 11 cm and tender.

For hepatitis C, it is 30–60 days, for hepatitis D 60–80 days (similar to HBV), and for hepatitis E 25–60 days.

- **Manifestation:** The disease has a relatively milder course in pediatric age group.

- **Hepatitis A:** Onset may be insidious or acute with fever, anorexia, malaise, nausea, vomiting, headache, upper abdominal pain with some hepatomegaly, constipation/diarrhea and high colored urine. This is followed by appearance of jaundice (Fig. 30.3) in 1–3 days. Jaundice may not appear at all in some children. But when it appears, other symptoms like fever and anorexia subside.
- **Hepatitis B:** Extrahepatic manifestations such as serum sickness, polyarteritis nodosa, glomerulonephritis (membranous/membranoproliferative), essential mixed cryoglobulinemia, pericarditis, myocarditis or pleural effusion are its cardinal feature.

About one-fourth cases have just little jaundice and pain abdomen. A few have rapidly fulminant course with hepatocellular failure and hepatic coma. Those who survive either recover completely or develop chronic hepatitis or postnecrotic cirrhosis later.

Differential Diagnosis

- Malaria (*falciparum*)
- Typhoid
- Leptospirosis
- Viral hemorrhagic fever
- Drug-induced hepatitis
- Infectious mononucleosis
- Autoimmune hepatitis
- Wilson disease
- Hemolytic jaundice
- In case of a newborn, diffuse hepatitis of herpes simplex, cytomegalic inclusion disease and toxoplasmosis must also be excluded.

Diagnosis

Diagnosis is mainly clinical. The following investigations are of value:

- Conjugate (direct) hyperbilirubinemia (serum bilirubin is as high as 10 mg).

- AST and ALT are remarkably high in the early course of the disease; alkaline phosphatase and lactate dehydrogenase (LDH) are only slightly raised.
- Erythrocyte sedimentation rate (ESR) is increased.
- Slight leucopenia with relative lymphocytosis. Occasionally, monocytosis to the extent of 25% may be present.
- Prothrombin time is usually within normal limits.
- Electrophoretic analysis shows high gammaglobulins, but normal albumin.
- Serologic tests are mandatory for identifying the exact type of viral hepatitis. Diagnosis of HAV depends on demonstration of raised titer of anti-HAV IgM antibody in serum by methods such as radioimmunoassay (RIA) or enzyme linked immunosorbent assay (ELISA) (Box 30.2).

Complications

- Acute liver failure
- Chronic liver disease (CLD)
- Aplastic anemia
- Acute pancreatitis
- Vasculitis like reaction
- Serum sickness
- Hemolysis in glucose 6 phosphate dehydrogenase (G6PD) deficiency subjects.

Treatment

Hepatitis A

- Bed rest (not “absolute”; uncomplicated cases do not need hospitalization) as long as jaundice is present and ESR remains high.
- Small, but frequent feeds of high carbohydrate diet; intravenous (IV) glucose (10–20%) in case of severe vomiting. Fats, in any form are poorly tolerated and should be avoided.
- Adequate vitamin supplements. Role of vitamins is only supportive. However, vitamin K is of definite value when prothrombin time (PT) is prolonged.
- Gammaglobulins
- Neomycin may be given in serious cases for sterilization of the gut.
- Lactulose, a nonabsorbable disaccharide, should be given as syrup, 10–50 ml/day (O), or its diluted form as retention enema every 6 hours. It lowers blood ammonia level by reducing microbial ammonia production and by trapping ammonia in acidic intestinal contents.

Box 30.2 Serology in viral hepatitis

- **HAV:** IgM, anti-HAV
- **HBV:** HBsAg. It appears quite early in the infection (though during a brief **window period**, it may not be detectable) and disappears soon
- **HCV:** Anti-HCV antibody, HCV RNA
- **HDV:** HBsAg, IgM, anti-HBC.

Abbreviations: IgM, immunoglobulin; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV hepatitis C virus; RNA, ribonucleic acid; HDV, hepatitis D virus.

- A benzodiazepine antagonist, flumazenil, claims to reverse early hepatic encephalopathy.
- Steroids must not be given since they increase the risk of chronicity and relapses. Their use just because they produce temporary sense of well-being and improvement in liver function is injudicious.
- Hepatotoxic drugs like chlorpromazine, paracetamol, etc. should be avoided. Phenobarbital, chloral hydrate or diazepam is good enough for sedation.

Hepatitis B

No special treatment is required, except in special situations such as fulminant hepatitis and chronic hepatitis which is discussed later.

Hepatitis C (Chronic)

Drug therapy with interferon and ribavirin is available.

Hepatitis E

Interferon and ribavirin may be of value.

Prevention

Hepatitis A

- Hepatitis A which is transmitted by feco-oral route and therefore, prevention is achieved by improving the food, water and personal hygiene and environmental sanitation.
- Passive immunization can be attained by administering gammaglobulin rich in anti-HAV antibodies (0.1 mL/kg) or specific anti-HAV gammaglobulin (0.05 mL/kg) intramuscularly (IM) to close contacts of a case of hepatitis A (as in a family; not school) or to a child moving to an endemic area.
- A vaccine (Havrix) for human use is now available. This highly safe and highly immunogenic vaccine (formaline-killed) has emerged as a major step in the prophylaxis of hepatitis A. A live attenuated hepatitis A vaccine too is now available. Also, See Chapter 10 (Immunization).

Hepatitis B

- Hepatitis B is transmitted via a parenteral route; prevention is achieved by avoiding contamination by infected blood or its products. Screening of blood donors is essential. Utmost care needs to be exercised while handling HBsAg positive material.
- Passive immunization can be achieved by administering specific anti-HBs gammaglobulins for short-term immediate protection in situations such as accidental needle prick, neonate of a HBsAg-positive mother, etc.
- HBV (Engerix-B, Shanvac-B, HBvac, Envac, Hepavax) provides active protection which is long-lasting though not immediate. This vaccine is the pioneering genetically engineered cancer immunization. For details, See Chapter 10 (Immunization).
- In order to provide immediate and long-lasting protection, it is advisable to combine specific anti-HBs gammaglobulins with vaccine.

592 Hepatitis C

For hepatitis C, prevention consists of limiting the use of potentially dangerous blood derivatives and preheating of antihemophilic factor.

Hepatitis D

For delta hepatitis, preventive measures are on the same lines as for hepatitis B.

Hepatitis E

Prevention consists of improving the hygienic and sanitary conditions in the same way as for hepatitis A.

Prognosis

Overall prognosis is good. Recovery is complete in 95% of cases. Only a small proportion of the cases die following development of fulminant hepatitis and hepatic coma. A small percentage may progress to chronic hepatitis.

ACUTE LIVER FAILURE

(Hepatic Encephalopathy, Fulminant Liver Failure)

Definition

Acute liver failure (ALF) is defined as a constellation of potentially reversible neuropsychiatric and neurological manifestations in a subject with advanced hepatic dysfunction and/or necrosis.

Etiopathogenesis

Box 30.3 lists causes of ALF. Various hypothesis put forward to explain central nervous system (CNS) manifestations are listed in Box 30.4.

Box 30.3 Causes of acute liver failure

Causative factors

- **Infections:**
 - **Viruses:** HAV, HBV, HCV, HDV, HEV, EBV, CMV, herpes virus, varicella zoster virus, dengue
 - **Bacteria:** *Salmonella typhi*, leptospira
 - **Protozoa:** Malarial parasite
 - **Drugs:** Paracetamol, isoniazid, rifampicin, pyrazinamide, sodium valproate, carbamazepine, ketoconazole, halothane
 - **Metabolic disorders:** Wilson disease, ICC, galactosemia, tyrosinemia, fructose intolerance, neonatal iron overload (hemochromatosis), Niemann-Pick disease (type C), mitochondrial cytopathies
 - **Vascular:** Budd-Chiari syndrome, acute circulatory failure
 - **Malignant (Infiltrative):** Leukemia, lymphoma, histiocytosis
 - **Toxins:** Copper, carbon tetrachloride and herbal agents.

Precipitating factors

- Massive GI bleed
- Too rapid abdominal tap
- CNS depressants (calmpose)
- Hypoxia
- Hypoglycemia
- Hypokalemia
- Septicemia
- High protein diet.

Abbreviations: CNS, central nervous system; GI, gastrointestinal; ICC, Indian childhood cirrhosis; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus, HBV, hepatitis B virus, HCV, hepatitis C virus, HDV, hepatitis D virus.

Box 30.4

Hypothesis for neurological manifestation in viral hepatitis

- **Hyperammonemia**, because of failure of the diseased liver to metabolize it to urea; causes neurotoxicity.
- **Complex interactions** between ammonia, fatty acids and methionine derivatives cause HE.
- **False neurotransmitters** (octopamine) replacing true neurotransmitters (dopamine).
- **Disproportionately high AAA concentration:** Imbalance of branched chain (leucine, isoleucine and valine) vs aromatic (phenylalanine, tyrosine, tryptophan) amino acids because of increased uptake of latter in hepatic dysfunction mediates CNS depression.
- **GABAergic hypothesis:** Failure of liver to detoxify GABA causes CNS manifestations.

Abbreviations: CNS, central nervous system; GABA, gamma amino butyric acid; AAA, aromatic amino acid; HE, hepatic encephalopathy.

Table 30.1: Clinical grading of HE

Stage	Symptoms	Signs	EEG changes
1.	Spans of lethargy euphoria; reversal of day-night sleeping; could be alert	Finds difficult to draw figures and perform mental tasks	Normal
2.	Drowsiness/agitation behavioral problems, wide swings in mood, disorientation	Asterix, incontinence, fetor hepaticus	Generalized slowing, q waves
3.	Stupor, but arousable, confused, incoherent speech	Asterix, hyper-reflexia, rigidity, extensor reflexes	Remarkably abnormal triphasic waves
4.	Coma	No asterix, flaccidity,	Remarkably abnormal bilateral slowing, d waves, electric-cortical silence
4a	Response to noxious stimuli	Areflexia	
4b	No response to noxious stimuli		

Abbreviations: HE, hepatic encephalopathy; EEG, electroencephalogram.

Clinical Grading

It is listed in Table 30.1.

Investigations

These include:

- Liver function test (LFT)
- Serum ammonia, blood sugar, serum electrolytes and blood gas analysis
- Infection screening
- Viral serologic markers
- Electroencephalogram (EEG) changes include theta waves in stage II and III, delta waves in stage IV and triphasic waves in stage V
- Visual-evoked potentials (VEP) have an edge in early detection, monitoring and differential diagnosis of hepatic encephalopathy (HE)
- Lumbar puncture is helpful in differential diagnosis.

Cerebrospinal fluid (CSF) alpha ketoglutarate and glutamine is usually raised in HE.

Management

General Measures

- Measures aimed at reducing the formation of ammonia include:
 - 10% dextrose through IV line
 - Elimination of protein from diet until sensorium reverts to normal
 - Bowel washes and 50% magnesium sulfate enema
 - Sterilization of gut employing oral or injectable ampicillin
 - Nasogastric aspiration
 - Lactulose (or lactitol), 10–50 mL every 2–4 hourly, until it produced 2–3 stools/day.
- Measures aimed at reducing cerebral edema include:
 - Raising the head end of the bed at 30° elevation (with head in neutral position)
 - Fluid restriction
 - IV mannitol bolus infusion (20%; 0.5–1 g/kg/dose) every 6–8 hourly or hypertonic saline (3–30%)
 - Hyperventilation
- Appropriate chemotherapy for superadded infection(s), including *Candida* and anaerobic infection
- **For controlling/preventing coagulopathy and GI bleed,**
 - IV vitamin K
 - Fresh frozen plasma
 - H₂ blockers (ranitidine), antacids, etc.
- **For controlling/preventing hypoglycemia,** IV dextrose (10%)
- **For controlling/preventing electrolyte imbalance** (hypokalemia, metabolic alkalosis), appropriate monitoring and correction
- **For respiratory failure,** oxygen and assisted ventilatory support
- **For seizures,** half of the standard dose of diazepam as a brief bolus IV infusion
- **For hepatorenal failure**
 - Restriction of sodium and fluid and, if the need be
 - Hemodialysis or peritoneal dialysis
 - Bioartificial liver support system pending liver transplantation may provide the liver time for regeneration
- **For hypotension,** dopamine infusion
- **For benzodiazepine excess-induced HE,** the antagonist, flumazenil, is of value
- Other conservative measures include:
 - Strict avoidance of sedatives
 - Administration of branched-chain amino acids (BCAA), bromocriptine, zinc and L-3,4-dihydroxy phenylalanine (L-dopa).
- **Liver transplantation and nonbiologic and biologic methods of hepatic support** are of considerable help in improving the prognosis.

Specific Measures

- **Paracetamol toxicity/poisoning:** N-acetyl cystine; liver transplantation

- **Amanita toxicity/poisoning:** N-acetyl cystine, sibinin, 593 crystalline penicillin (penicillin G)
- **Mitochondrial cytopathy:** Carnitine, vitamin E, coenzyme Q10
- **Herpes simplex:** Acyclovir (as high a dose as 50–60 mg/kg/day for 3 weeks)
- **Hereditary fructose intolerance:** Fructose-free diet
- **Galactosemia:** Galactose plus lactose-free diet
- **Tyrosinemia:** Nitisinone; avoidance of phenylalanine plus tyrosine-containing foodstuffs
- **Neonatal hemochromatosis:** Prenatal intravenous immunoglobulin (IVIG), postnatal exchange blood transfusion; chelation therapy; antioxidants

Prognosis

With modern intensive care, survival is around 30–50%. With liver transplantation, survival has gone up to 60–70%.

CHRONIC LIVER DISEASE (CLD)

Definition

The term is employed for a wide spectrum of liver disorders with persistent inflammation of liver tissue which, unless treated, is likely to progress to end-stage liver disease (ESLD) in the form of cirrhosis or carcinoma.

Tentatively, the disease process should have been present for at least 3–6 months in case of hepatitis B and C, are the most frequent causes. In other etiologic conditions, irreversible damage to liver may have already occurred by the time the child presents with some manifestations of liver disease.

It is estimated that around one-third of hepatobiliary disorders fall under this umbrella. All types of chronic hepatitis come under this category. In fact, the large chunk of CLD is constituted by chronic hepatitis. Remaining conditions include hepatic fibrosis and cirrhosis. Box 30.5 lists the causes of CLD.

Box 30.5 Etiology of chronic liver disease

- **Neonatal cholestasis syndrome:** Biliary atresia, neonatal hepatitis, choledochal cyst, Watson-Alagille syndrome, PFIC
- **Infectious:** Hepatitis B, hepatitis C, hepatitis D and others
- **Autoimmune liver disease:** Autoimmune hepatitis
- **Metabolic:** Wilson disease, alpha-1-antitrypsin deficiency, glycogen storage disease, galactosemia, Gaucher disease, Niemann-Pick disease, Wolman disease, Zellweger syndrome, cystic fibrosis,
- **Drugs:** INH, ketoconazole, methyldopa, dantrolene, nitrofurantoin, amiodarone, methotrexate, calcium channel blockers
- **GI disorders:** IBD, celiac disease
- **Hepatobiliary disorders:** Biliary atresia
- Venous congestive/vascular problems
- **Miscellaneous:** Parasitosis, polycystic disorders of kidney and liver, histiocytosis, chronic liver abscess, ICC, hypervitaminosis A, TPN, NAFLD, NASH
- Cause undetermined (Cryptogenic/idiopathic).

Abbreviations: NASH, nonalcoholic steatohepatitis; NAFLD; nonalcoholic fatty liver disease; TPN, total parenteral nutrition; ICC, Indian childhood cirrhosis; INH, isoniazid; PFIC, progressive familial intrahepatic cholestasis; IBD, inflammatory bowel disease; GI, gastrointestinal.

594 CHRONIC HEPATITIS

Definition

Chronic hepatitis (CH) is defined as continuing (ongoing) inflammation of liver parenchyma for at least 3–6 months. If it fails to resolve with or without treatment, it is likely to progress to an irreversible and severe chronic liver disease that finally terminates as cirrhosis/ESLD. The presence of continuing hepatic inflammation is confirmed by raised hepatic transaminase levels.

Etiopathogenesis

Besides the persistent viral infection (HBV, HBC, HBD, infrequently HBE; never HBA), drugs, metabolic liver injury, autoimmune mechanism or unknown factors may be responsible for its occurrence in a significant proportion of cases.

The exact modus operandi of pathogenesis is not known. Demonstration of antinuclear and antismooth muscle antibodies in serum and multisystem involvement in the form of arthropathy, rashes, thyroiditis and Coombs-positive hemolytic anemia strongly hint at an autoimmune process. In pediatric practice, leading causes of CH are hepatitis B, hepatitis C, autoimmune hepatitis and metabolic liver disease.

Staging and Grading

Currently, the trend is to stage and grade CH based on the fibrosis and neuroinflammation respectively, in the liver biopsy (Tables 30.2 and 30.3).

Clinical Features

Different modes of onset/presentation of CH include:

- Acute viral hepatitis-like with prolongation of symptoms (Wilson disease, alpha-1-antitrypsin deficiency, autoimmune hepatitis)

Table 30.2: Staging of chronic hepatitis based on fibrosis

Stages	Fibrosis	Architecture
Stage 1	None or minimal	No significant enlargement of portal tracts; no septa
Stage 2	Dominantly periportal	Enlarged portal tracts, periportal fibrosis or portal to portal septa but no architectural distortion
Stage 3	Septal	Significant septal fibrosis and architectural distortion or certain cirrhosis
Stage 4	Cirrhotic changes	Probable or certain cirrhosis

Table 30.3: Grading of chronic hepatitis based on necroinflammation

Grades	Portal/periportal necroinflammation	Lobular necroinflammation
Grade 0	None or minimal	None
Grade 1	Portal inflammation	Only inflammation
Grade 2	Mild limiting plate necrosis	Severe focal cell damage
Grade 3	Moderate limiting plate necrosis	Severe focal cell damage
Grade 4	Severe limiting plate necrosis	Bridging necrosis



Fig. 30.4: Chronic liver disease. Note the enlarged liver in this girl with chronic hepatitis. The liver was enlarged (5 cm below costal margin; span 13 cm) and unusually firm.

- Chronic insidious type with portal hypertension
- Asymptomatic type—the disease is picked up by high index of suspicion when investigating for some other disorder or when liver is found to be unusually firm (Fig. 30.4).

Clinical clues favoring CH include a history of neonatal cholestasis syndrome, CLD in the family, relapse or persistence of symptoms of acute hepatitis over at least 3 months, a small and shrunken liver with relative enlargement of the left lobe, hard or nodular liver, splenomegaly, edema and/or ascites, upper gastrointestinal bleed, failure to thrive (FTT), muscle wasting, vitiligo, arthritis, spider nevi, facial telangiectasia and extrahepatic manifestations of autoimmune hepatitis or Wilson disease.

Diagnosis

Diagnosis is by:

- Liver function test (serum bilirubin, including direct and indirect, AST, ALT, alkaline phosphatase) to assess status of liver.
- Ultrasonography of abdomen, upper GI endoscopy and Tc 99m hepatic scan to assess presence of portal hypertension and cirrhosis.
- Liver biopsy is the gold standard for confirmation of pathological diagnosis.

Investigations

Investigations required for identifying exact cause include:

- Viral markers
- Autoantibodies
- Alpha-1-antitrypsin
- Copper studies
- Aminoacidogram
- Specific metabolic studies
- Toxoplasma, other agents, rubella, cytomegalovirus and herpes simplex (TORCH) profile for influenza-like illness (ILI) infections.

Table 30.4: Specific (definitive) therapy in chronic hepatitis

Condition	Therapy	Other measures
Autoimmune chronic active hepatitis (CAH)	Steroids, azathioprine	
Wilson disease	Penicillamine	Avoid copper-rich foods, e.g. liver, shellfish, mushroom, chocolates, nuts
Hepatitis B and C	Interferon	
Galactosemia	Galactose-free (milk-free) diet	

Management

Specific therapy is possible in only a minority of the subjects (Table 30.4). Complications such as upper GI bleed, ascites, peritonitis and encephalopathy should be appropriately treated. Supportive care should be in the form of much higher intake of energy (1.5–2 times the normal requirements), 4 g/kg/day of protein and fat soluble vitamins (5–10 times the normal requirements).

Prognosis

It depends on the type and the treatment offered. Generally speaking, severe chronic active hepatitis, despite treatment, ends up in ESLD with cirrhosis or hepatocellular carcinoma.

METABOLIC LIVER DISEASE

Definition

Metabolic liver disease is defined as CLD as a result of persistent metabolic abnormalities with Wilson disease on top and alpha-1-antitrypsin deficiency at the bottom in frequency. It accounts for nearly 1/5th cases of CLD.

Etiology

Box 30.6 lists important causes of metabolic liver disease.

Clinical Features

Clinical presentation is nonspecific with manifestations varying with the individual causative condition.

Box 30.6 Etiologic conditions in metabolic liver disease

- **Metal metabolism disorders:** Wilson disease, Indian childhood cirrhosis (ICC), neonatal hemochromatosis
- **Bile acid/bilirubin metabolism disorders:** Bile acid-benign recurrent intrahepatic cholestasis, progressive familial intrahepatic cholestasis I, II, III. Bilirubin–Dubin–Johnson syndrome, Crigler–Najjar syndrome type I, II, Gilbert syndrome, Rotor syndrome
- **Carbohydrate metabolism disorders:** Galactosemia, glycogen storage disease type I, III, VI, hereditary fructose intolerance
- **Protein metabolism disorders:** Tyrosinemia, defects of urea cycle
- **Fat metabolism disorders:** Gaucher disease, Niemann–Pick disease type C, Wolman disease
- **Miscellaneous disorders:** Cystic fibrosis, alpha-1-antitrypsin deficiency.

Box 30.7 Clinical clues to the diagnosis of metabolic liver disease

- Consanguinity, positive family history, death of a sibling (Wilson disease)
- Recurrent episodes of an apparently minor illness resulting in unexpected deterioration
- Unexplained encephalopathy, hypoglycemia, acidosis, hyperammonemia, etc. with recurrent episodes (mitochondrial hepatopathies, organic acidurias, urea cycle defects)
- Specific food intolerance/aversions e.g. sugar (hereditary fructose intolerance), protein (defects of urea cycle)
- Rickets with unusual odor from urine (tyrosinemia)
- Developmental delay with multisystem involvement (mitochondrial hepatopathies)
- Fatty infiltration of liver.

Diagnosis

Clinical Clues

High index of suspicion contributes to clinching the diagnosis after appropriate investigations. Box 30.7 lists the clinical clues to the diagnosis of metabolic liver disease.

Investigations

- Complete blood picture (CBP)
- Arterial blood gases (ABG) with lactate, amino acids, electrolytes, glucose and ammonia
- Plasma and urine amino acids and organic acids
- Urine for ketone bodies and sugar
- Liver biopsy
- Enzyme assay
- Genetic mutation analysis.

Treatment

- Specific therapy
 - Chelation with penicillamine in Wilson disease
 - Dietary modification for galactosemia for phenylketonuria (PKU)
 - Liver transplantation
- Supportive and symptomatic therapy
 - Optimal nutrition with supplements of vitamins, micronutrients, antioxidants, immunonutrients, etc.
 - Correction of hypoglycemia
 - Treatment of coagulopathies
 - Treatment of ascites
 - Appropriate vaccines
 - Monitoring for hepatocellular carcinoma.

WILSON DISEASE

(Hepatolenticular Degeneration)

Wilson disease is an inborn error of metabolism and a major cause of metabolic liver disease and CLD in India with a prevalence of around 1 in 40,000.

Definition

Wilson disease, an autosomal recessive disorder, is characterized by an excessive increase in copper deposition in body organs and tissues due to inability of the liver to metabolize the normally absorbed dietary copper.

596 Etiopathogenesis

Precisely, copper is neither incorporated into apoceroloplasmin nor secreted into bile. As a result, it accumulates in liver, brain, cornea, kidneys and many other body tissues and systems.

Clinical Features

Manifestations appear after 4–5 years of age and may be predominantly hepatic in early childhood and neurological in later age group (adolescence).

- **Hepatic manifestations:** Acute self-limiting hepatitis, CAH, ALF and cirrhosis.
- **Neurological manifestations:** Dystonia, choreoathetosis, seizures.
- **Psychiatric manifestations:** Behavioral problems, clumsiness and deterioration in scholastic performance.
- **Renal manifestations:** Renal rickets.
- **Ophthalmic manifestations:** Keyser-Fleischer (KF) rings in cornea.
- **Growth:** FTT.

Diagnosis

A high index of suspicion paves the way for reaching the diagnosis in this slow evolving disease. Investigations include:

- **Serum ceruloplasmin:** Less than 20 mg/dL level is suggestive.
- **24-hour urinary copper excretion:** More than 100 µg/day is suggestive.
- **Liver biopsy for hepatic copper content:** More than 250 µg/g dry weight of liver is nearly diagnostic. This should be considered gold standard.
- **Mutational diagnosis:** Of value in screening family members of an index case of Wilson disease.

Treatment

Treatment options are:

- Dietary restriction of copper in the form of avoidance of organ meat (liver), nuts, chocolates, etc.
- Drugs like penicillamine, trientine and zinc as chelating therapy.
- Orthotopic liver transplantation.

GLYCOGEN STORAGE DISEASES (GSD)

- **Type I GSD** is (von Gierke disease), due to G6PD deficiency, is characterized by doll-like facies, truncal obesity, massive hepatomegaly, nephromegaly, hypoglycemia, seizures, FTT, hyperuricemia, hypertriglyceridemia and lactic acidosis.
- **Type II GSD** is an abnormality of debrancher enzyme—amylo-1,6 glucosidase. It is characterized by hepatosplenomegaly, hypoglycemia, fibrosis in liver and raised transaminases with complication of myopathy.
- **Type IIIa** is predominantly a myopathy whereas **type IIIb** is predominantly liver disease.
- **Type IV GSD;** defect in glycogen branching enzyme is characterized by CLD, portal hypertension and

hepatic decompensation. Though normal at birth, hepatomegaly and FTT manifest in infancy followed by splenomegaly in the second year. Death occurs by 3 year of age by cirrhosis

- **Type VI and IX GSD;** defect in hepatic phosphorylase system, present in preschool children with asymptomatic hepatomegaly. It is by and large a benign condition. Therapy in GSD revolves around prevention hypoglycemia by frequent daytime feeding with slowly absorbed carbohydrates such as starch, glucose polymers and continuous nocturnal feeding. Liver transplantation may benefit Type IV GSD.

GALACTOSEMIA

- Though three types are known, classical galactosemia is caused by deficiency of galactose 1 phosphate uridyl transferase (GALT).
- Clinical features include vomiting/diarrhea (starting within a few days of initiating milk), jaundice (in first few week of life), hepatomegaly, hypoglycemia, ascites, liver failure, coagulopathy, cataracts, *Escherichia coli* sepsis and cirrhosis.
- Treatment rests on elimination of dietary galactose.
- Prenatal diagnosis is available.

AUTOIMMUNE LIVER DISEASE

Definition

It is defined as an autoimmune involvement of the liver that may manifest as acute autoimmune hepatitis, insidious-onset liver disease or CLD. Diseases that fall under this umbrella are:

- Autoimmune hepatitis
- Autoimmune sclerosing cholangitis
- Post-transplant autoimmune hepatitis.

Types

- **Type 1 (75% cases):** It is characterized by presence of antinuclear antibodies and/or antismooth muscle antibodies.
- **Type 2 (25% cases):** It is characterized by anti-liver, kidney microsomal antibodies.

Characteristic Features

- Circulating autoantibodies
- Necroinflammatory histology in liver biopsy
- Response to immunosuppressive therapy.

Clinical Features

- **Acute-onset (acute viral hepatitis-like):** Nausea, vomiting, jaundice, anorexia and malaise.
- **Insidious-onset liver disease:** Prolonged or waxing-waning jaundice, easy fatigability spread over several months.
- **Chronic-onset liver disease:** Jaundice, ascites, splenomegaly, bleeding esophageal varices and hepatic encephalopathy.

Diagnosis

Diagnosis rests on the following parameters in a case in which known causes of CLD such as viral hepatitis and Wilson disease stand excluded:

- Presence of autoantibodies
- Demonstration of elevated gammaglobulins and IgG
- Characteristic liver histology on biopsy
- Appropriate response to immunosuppressive therapy.

Treatment

- Medical therapy
 - **First line agents:** Steroids and azathioprine
 - **Second line agents:** Cyclosporine and mycophenolate.
- Liver transplantation in case of ESLD.

NONALCOHOLIC FATTY LIVER DISEASE/STEATOSIS

Definition

Nonalcoholic fatty liver disease (NAFLD) is defined as macrovesicular steatosis in hepatocytes provided that other causes of fatty liver have been excluded. When inflammation with fibrosis is also present, it is termed as **nonalcoholic steatohepatitis (NASH)**.

Etiopathogenesis

The crux of the vulnerable background is obesity as a result of diet that is rich in saturated fats and refined carbohydrates, and a sedentary lifestyle plus hereditary hyperinsulinemia. Box 30.8 list important causes.

Clinical Features

In symptomatic cases, manifestations include abdominal discomfort/pain. Signs include:

- Generalized obesity
- Splanchnic
- Hepatomegaly
- Occasionally splenomegaly
- Dark pigmentation in skinfolds and axillae (acanthosis nigricans) in 1/3–1/2 subjects.

Diagnosis

- **NAFLD:** Based on raised serum ALT, fatty liver on radiology and liver biopsy.

Box 30.8 Etiology of NAFLD/NASH

- **Genetic disorders:** Prader-Willi syndrome, Laurence-Moon-Biedl syndrome
- **Metabolic disorders:** Lipodystrophy syndrome, galactosemia, glycogen storage disease, hereditary fructose intolerance, Alstrom syndrome, polycystic ovary syndrome
- **Medication:** Steroids, calcium channel blockers, methotrexate, amiodarone and perhexiline
- **Tumors:** Craniopharyngioma
- **Miscellaneous:** TPN, jejuniojejunal bypass.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; TPN, total parenteral nutrition.

* Following a significant “bleed”, spleen may temporarily shrink, causing reduction in its size

- **NASH:** Based on raised ALT as well as AST, high fasting serum insulin, hyperglycemia and liver biopsy. **597**

Treatment

- Life style changes aimed at weight reduction, especially waist circumference which is directly related to visceral obesity. This cuts down the insulin resistance as well.
- Pharmacotherapy—vitamin E, ursodeoxycholic acid and metformin.

Prevention

Prevention of obesity is the best approach for safeguarding against NAFLD and NASH.

PORTAL HYPERTENSION

Portal hypertension, a frequent problem, is said to exist when pressure in the portal venous system (normal variation 5–10 mmHg) exceeds 12 mmHg.

Two types are known—(1) intrahepatic and (2) extrahepatic, existing in the ratio of 30:70 in India.

Intrahepatic Portal Hypertension (IHPH)

Etiology

- Cirrhosis is undoubtedly its most common cause.
- Portal vein thrombosis is a relatively common cause of portal hypertension. This almost always follows umbilical sepsis and repeated exchange transfusions using the umbilical vein.
- Indian childhood cirrhosis once a common cause of IHPH, stands nearly eliminated now.
- Jamaican VOD causes widespread occlusion of small and medium hepatic veins and early development of portal hypertension. The disease is rare in India.
- Budd-Chiari syndrome, involving main hepatic vein from various causes like thrombosis, vasculitis, sepsis or tumor, is rare in childhood.
- Congenital hepatic fibrosis, usually in association with renal anomalies, is a rare cause of portal hypertension.

Clinical Features

- Ascites with abdominal distention (usually without caput medusae or varicose veins), hepatosplenomegaly* (spleen bigger than liver) and pain abdomen are the most common presenting features.
- Hematemesis, melena and jaundice are less frequently seen.
- Thrombocytopenia due to hypersplenism may develop.
- Application of pressure over liver does not cause distention of the jugular vein, the so-called **hepatojugular reflex**.

Diagnosis

- Liver function tests, though abnormal, are not quite helpful in localizing the obstruction.
- Upper gastrointestinal endoscopy, barium swallow, ultra-sonography (with Doppler studies) and portal

angiography (with computerized axial tomography {CAT} scan or MR images) may show esophageal varices.

- Hematological investigations are required to find out the adverse effects of repeated hemorrhages and the current hematological status of the patient.
- Liver biopsy is of great help to establish the diagnosis of the underlying disease process.
- The most reliable investigation is the splenic venoportogram which bears open the whole portal system in the X-rays, ultrasonography, CT or MRI so that the site of obstruction can be located.

Treatment

- Initial management of variceal bleed consists of crystalloid infusion, vitamin K, nasogastric intubation, H₂ receptor antagonist (ranitidine) (IV).
- If the patient is significantly anemic and/or having large hematemesis, blood transfusion is usually needed. To control persistent bleeding from esophageal varices, endoscopic sclerotherapy, intraesophageal balloon catheter, Sengstaken tube, is passed or IV vasopressin, somatostatin or a somatostatin analogue (octreotide) administered.
- Propranolol therapy has been found to be of value for prevention of recurrent gastrointestinal bleeding. The beneficial effect of this therapy appears to be from reduced portal pressure secondary to decreased cardiac output.
- To check distressing ascites, it may become appropriate to give a diuretic like furosemide. Such patients run the risk of going into hypernatremia and hypokalemic alkalosis. Remember to maintain the fluid and electrolyte balance.
- The eventual answer is a bypass operation to join the portal vein with a systemic vein, provided that cirrhosis has not already developed.

Prognosis

It depends on the underlying cause and the treatment offered. Without treatment, hepatic failure, coma and death are a rule. Even with treatment, portal hypertension associated with cirrhosis (as a cause or effect) ends in a similar fashion. Early surgical intervention in hepatic vein thrombosis or Budd-Chiari syndrome (not resulting from malignancy) gives good results.

Extrahepatic Portal Hypertension

Etiology

Its common causes are umbilical sepsis during neonatal period (Fig. 30.5), umbilical vein catheterization and dehydration, leading to splenic or portal vein thrombosis. Other causes include congenital splenic or portal vein anomalies and compression of portal vein by lymph glands and bands. The obstruction can be anywhere between hilum of the liver to the hilum of the spleen.

Clinical Features

- Hematemesis, melena and abdominal distention due to ascites are the most common presenting symptoms,

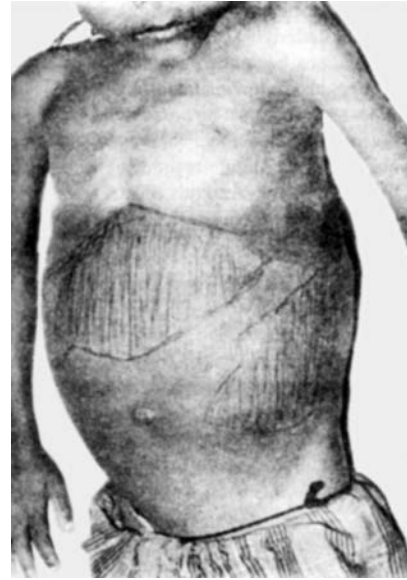


Fig. 30.5: Extrahepatic portal hypertension. Note hepatosplenomegaly and abdominal distention with moderate ascites. There was a positive history of umbilical sepsis (during neonatal period) which may have caused portal vein thrombosis.

particularly in a child who had otherwise been doing well.

- A respiratory infection may cause severe cough and thereby precipitate a bout of hematemesis due to bleeding from esophageal varices.
- Ascites may show fluctuation; it usually follows an episode of bleeding.
- History of a severe infection, umbilical sepsis, dehydration or umbilical vein catheterization for exchange transfusion (prolonged and difficult) in neonatal period or early infancy is often traceable. Splenomegaly with or without hepatomegaly is the most constant sign.

Diagnosis

- Liver function tests and liver biopsy are essentially normal.
- Upper gastrointestinal endoscopy or barium swallow may reveal esophageal and gastric varices in 80% of the cases.
- Ultrasound is an excellent screening test for defining the site of the disease.
- Confirmation of the diagnosis is by demonstration of high splenic pulp pressure, i.e. above the cut-off level of 12 mmHg and the block by simultaneous splenic portography.

Treatment

Medical treatment to control the disease has its place. This helps in at least two ways. Firstly, chances of surgical shunts appear to improve as the child gets older. Secondly, he may develop a decompressive shunt so as to prevent hemorrhage from the varices.

The medical measures have already been underscored. Remember to treat anemia with hematinics, to avoid drugs like aspirin and to make sure that the child takes soft food in small amounts but at frequent intervals.

Sclerotherapy, i.e. direct injection of varices is employed by some in children less than 10 years of age prior to operation or when other measures have failed to control bleeding. Simultaneous splenectomy and splenorenal shunts are the most popular surgical procedures but these have their limitations. If portal vein is spared by the disease process, the most satisfactory procedure would be portocaval anastomosis.

NEONATAL CHOLESTASIS SYNDROME (NCS)

By definition, it is a prolonged elevation of serum levels of conjugated bilirubin beyond first 14 days of life. In India, it is estimated to constitute 30% of the hepatobiliary disorders.

Etiology

A large number of conditions may cause neonatal cholestasis (Box 30.9). Experience in India and other countries of Southeast Asia indicate that around 67% cases are equally distributed between extrahepatic and intrahepatic etiology. The left over 33% cases are idiopathic neonatal hepatitis. Two most likely mechanisms are virus-induced hepatic insult and metabolic liver disease. Irrespective of the cause, clinical manifestations of all forms of cholestasis are by and large similar.

Clinical Features

Manifestations of neonatal cholestasis include:

- Persistent icterus with high-colored urine and clay-colored or light (alcoholic) stools.
- Hepatomegaly (Fig. 30.6) as a result of poor bile flow because of liver cell injury or bile duct obstruction.
- Bleeding diathesis as a result of vitamin K insufficiency and hypoprothrombinemia because of hepatic synthetic dysfunction.

Box 30.9 Etiology-cum-differential diagnosis of neonatal cholestasis

- **Infections:** Hepatitis A, B and C, STORCH group of infections, septicemia/sepsis.
- **Metabolic:** Galactosemia, fructosemia, glycogenosis IV, alpha-antitrypsin deficiency, cystic fibrosis, hypothyroidism, hypopituitarism, Gaucher disease, Niemann-Pick disease, Wolman disease, tyrosinemia, Zellweger (cerebrohepatorenal) syndrome, bile acid metabolic defects, neonatal iron storage disease, copper overload (ICC), arginase deficiency, mitochondrial DNA depletion.
- **Genetic/Chromosomal:** Down syndrome, Trisomy E, leprechaunism.
- **Intrahepatic:** Idiopathic neonatal hepatitis, intrahepatic cholestasis, intrahepatic biliary hypoplasia.
- **Extrahepatic:** Extrahepatic biliary atresia, choledochal cyst, inspissated bile syndrome (bile/mucus plug, bile duct stenosis, mass (neoplasia, stone).
- **Miscellaneous:** Drugs, TPN, histiocytosis, shock, enteritis, intestinal obstruction, neonatal lupus erythematosus, myeloproliferative disease.

Abbreviations: STORCH, syphilis, toxoplasmosis, other agents, cytomegalovirus and herpes simplex; ICC, Indian childhood cirrhosis; DNA, deoxyribonucleic acid; TPN, total parenteral nutrition.



Fig. 30.6: Neonatal cholestasis syndrome. Note massive ascites on top of cirrhotic liver secondary to extrahepatic biliary atresia (EHBA).

Box 30.10 Investigative work-up for suspected neonatal cholestasis

- **Blood:** Total and fractional bilirubin, transaminases, alkaline phosphatase and prothrombin time.
- **Serology:** Evidence of infections (HBsAg, specific viral serology, VDRL).
- **Blood, urine, spinal fluid cultures:** For bacteria, herpes simplex, CMV, enteroviruses.
- **Ultrasonography:** It is particularly of value in identifying surgically correctable conditions such as choledochal cysts.
- **Radionuclide hepatobiliary scintigraphy:** It is of great value in excluding EHBA.
- **Liver biopsy:** It is important in differentiating between surgical and nonsurgical cases of cholestasis.

Abbreviations: VDRL, venereal disease research laboratory; CMV, cytomegalovirus; EHBA, extra hepatic biliary atresia, HBsAg, hepatitis B surface antigen.

Diagnosis

Since clinical features hardly provide any concrete clues regarding the underlying cause of cholestasis, a recourse to investigations becomes mandatory (Box 30.10). Nevertheless, the following important points in history and clinical work-up must be borne in mind:

- Presence of cataract and cherry-red spots point to galactosemia and lipid storage disease, respectively.
- Detection of chorioretinitis means an intrauterine infection like toxoplasmosis, rubella, CMV.
- Higher birth weight, earlier onset of icterus with clay-colored stools, coexistence of congenital malformations and absence of familial occurrence are points in favor of extrahepatic biliary atresia (EHBA) rather than neonatal hepatitis.

Management

- **Nutritional support** is central to any treatment offered to infants with cholestasis. It is advisable to provide medium-chain triglycerides (coconut oil) for enhancing fat and energy assimilation and fat soluble vitamins to makeup for their poor absorption. Anorexic infants should receive nasogastric feeding.
- **Replacement therapy** may be warranted in the form of fat-soluble vitamins (A, E, D and K), water-soluble vitamins and micronutrients (calcium, phosphate, zinc).

- 600 ■** Treatment of pruritus is in the form of phenobarbital, choleretics (ursodeoxycholic acid) or bile acid binders (cholestyramine), rifampicin, naloxene, terfenadine, or 3–4 minute/day phototherapy with ultraviolet or infrared rays.
- **Chemotherapy** for sepsis, especially in the presence of ascites and ESLD.
 - **Appropriate treatment of associated complications** such as variceal bleed (endoscopic sclerotherapy), ascites, hepatic encephalopathy, renal failure.
 - **Surgical treatment** is indicated in EHBA and choledochal cyst, provided that liver damage has not advanced to the stage of cirrhosis.
 - **Liver transplantation** may be done in ESLD (liver failure) in case the family can afford it.

A practical algorithm has been suggested as per the Indian Academy of Pediatrics (IAP) Subspecialty Chapter of Pediatric Gastroenterology (Fig. 30.7).

Prognosis

On account of delayed diagnosis and referral in a vast majority of infants with NCS, prognosis is unfavorable. In idiopathic neonatal hepatitis of sporadic variety, 60–70% cases recover whereas in the familial variety, recovery occurs in only 20–30% cases, the remaining cases ending up as CLD with cirrhosis.

EXTRAHEPATIC BILIARY ATRESIA

See Chapter 46 (Pediatric Surgery).

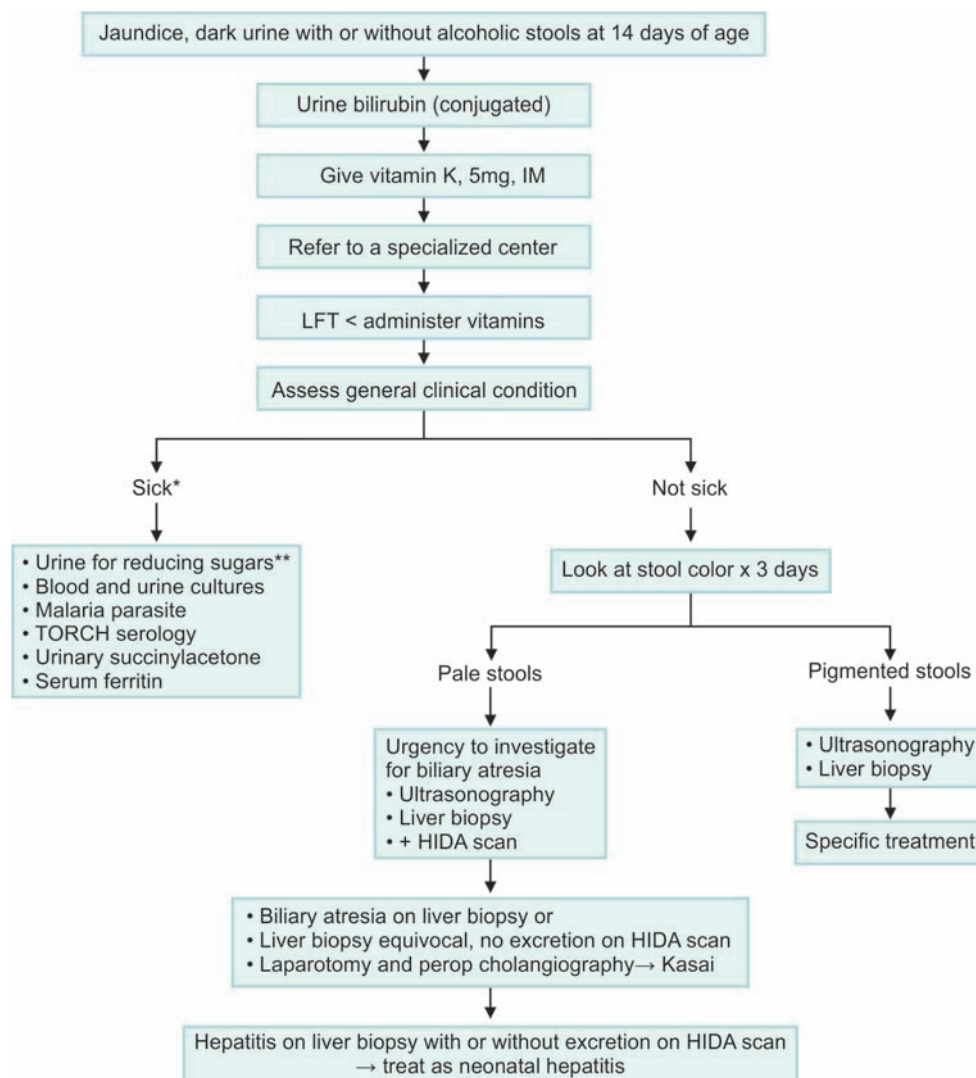


Fig. 30.7: Algorithm on approach to neonatal cholestasis syndrome (NCS).

Abbreviations: HIDA, hepatobiliary iminodiacetic acid; TORCH, toxoplasma, other agents, rubella, cytomegalovirus and herpes simplex virus; LFT, liver functional test; IM, intramuscularly; CMV, cytomegalovirus; UTI, urinary tract infection.

* Babies with NCS due to infections of herpes, toxoplasmosis and rarely CMV may be sick, look for their extrahepatic manifestations. Stop milk feeds till galactosemia is ruled out. In febrile babies, look for malarial parasite, sepsis and UTI.

** This is to look for galactose in urine while on milk feeds. If reducing substances are positive, check urine samples with glucose stick. If negative, most likely reducing substances in urine are due to galactose. Treat as galactosemia.

CHOLEDOCHAL CYST

See Chapter 46 (Pediatric Surgery).

CHOLECYSTITIS

Cholecystitis with Cholelithiasis

When cholecystitis occurs in association with cholelithiasis, some predisposing factors such as chronic hemolytic disease (thalassemia, sickle cell anemia and red blood cell enzymopathies), obesity, Wilson disease, ileal disease, bile acid malabsorption, etc. are usually present. Gallstones from a mixture of cholesterol, bile pigment, calcium and inorganic matrix, are the most common variety followed by pure cholesterol or pure bile stones.

Clinical features of cholecystitis with cholelithiasis include recurrent colicky pain in the right upper quadrant of abdomen, intolerance for fatty foods, pyrexia and a palpable lump. Ultrasound is the investigation of choice for gallstone detection. Cholecystectomy is curative. Alternatively, oral chenodeoxycholic acid or extracorporeal lithotripsy may be employed for dissolution of the stones.

Acute Acalculous Cholecystitis

Acute acalculous cholecystitis may develop secondary to infections, e.g. streptococcus group A and B, Gram-negative pathogens like *Salmonella*, *Lambliia giardia*, *Ascaris lumbricoides*, etc., abdominal trauma, periarteritis nodosa and other systemic vasculitis, and Kawasaki disease.

Clinical features include right upper quadrant or epigastric pain, nausea, vomiting, pyrexia and jaundice. Examination reveals right upper quadrant guarding and tenderness. Diagnosis is by ultrasound that shows an enlarged and thick walled gallbladder without stones. Supportive laboratory findings are high total leukocyte count (TLC), serum alkaline phosphatase and conjugated bilirubin. Treatment revolves round therapy for primary infection and cholecystectomy in some cases.

DRUG-INDUCED LIVER INJURY

Liver is remarkably vulnerable to insult from certain drugs because of its vital role in drug metabolism. Administration of two hepatotoxic drugs increases the chances of liver damage.

Types

- **Direct (dose-dependent) hepatotoxicity:** It results from agents that are directly hepatotoxic and disrupt the hepatic cells, cause microsomal and mitochondrial injury and damage the canalicular apparatus. Examples of agents in this category are paracetamol, chlorpromazine, ferrous sulfate, hormones and antimetabolites.
- **Indirect (dose-independent) hepatotoxicity:** It results as an expression of patient's vulnerability due to hypersensitivity or formation of hepatotoxic metabolites (idiosyncrasy). Both hypersensitivity and abnormal metabolites lead to idiosyncratic reactions. In the former, allergic symptoms like rash, fever, eosinophilia and granuloma

in the liver are common. Sensitization (latent) period is 1–4 weeks and 2–52 weeks, respectively. Examples are propoxyphene, nitrofurantoin, mepacrine, chlordiazepoxide, rifampicin and isoniazid.

Diagnosis

For diagnosis of drug-induced hepatotoxicity, the following points should be borne in mind:

- History of drug exposure.
- Manifestations compatible with certain drugs.
- Hypersensitivity symptoms such as rash, fever and eosinophilia in a subject with abnormal LFTs.
- Recurrence of symptoms and hepatic dysfunction following a test dose of the drug in patients in whom the drug needs to be continued.

Management

It consists of immediate withdrawal of the offending drug along with high protein, high calorie diet, cholestyramine or phenobarbital to relieve pruritus and jaundice. Symptoms resolve within days and biochemical liver function within weeks. Rarely, portal hypertension and fulminant hepatitis may occur in advanced cases.

HEPATOMEGALY

In neonates and infants, liver may be normally palpable up to 1–2 cm below the costal margin on account of narrowing of the costal angle. In emphysema, bronchiolitis and pneumothorax, it may be pushed down, thereby becoming palpable though not enlarged. In visceroptosis secondary to laxity of ligaments and muscles in rickets, liver may descend down and become palpable without enlargement. It is, therefore, important to interpret the palpability of liver below the costal margin carefully.

Etiology

Hepatomegaly, a common problem in pediatric practice may be caused by a large number of conditions (Box 30.11).

Approach to Evaluation

Evaluation of hepatomegaly should include a good history and clinical examination together with liver function tests, ultrasonography and other investigations depending on the merits of each case.

History and Physical Examination

Enquiry should focus on history of jaundice, pruritus, anorexia, blood transfusions, injections/pricks, familial/sibling involvement, etc. More significant than sheer palpability of the liver is the measurement of liver span (Box 30.12) for the enlargement.

Additional information needed is—shape, consistency, surface characters, border, tenderness, murmurs or bruit, and any accompanying masses. There is a well-known kinship in hepatomegaly and splenomegaly may be as a result of:

Box 30.11 Differential diagnosis of pediatric hepatomegaly**Newborn**

- **Infections:** Intrauterine TORCH group of infections, neonatal hepatitis, septicemia/sepsis, malaria
- **Metabolic/Storage:** Galactosemia, fructosemia, glycogenesis IV, alpha-1-antitrypsin deficiency, cystic fibrosis, hypothyroidism, hypopituitarism, Gaucher disease, Niemann-Pick disease, Wolman disease, tyrosinemia, Zellweger (cerebrohepato renal) syndrome, bile acid metabolic defects, neonatal iron storage disease, copper overload (ICC), arginase deficiency, mitochondrial DNA depletion
- **Genetic/Chromosomal:** Down syndrome, Trisomy E, leprechaunism
- **Intrahepatic:** Idiopathic neonatal hepatitis, intrahepatic cholestasis, intrahepatic biliary hypoplasia
- **Extrahepatic:** Extrahepatic biliary atresia, choledochal cyst, inspissated bile syndrome (bile/mucus plug) bile duct stenosis,
- **Miscellaneous:** CCF, drugs, TPN, histiocytosis, shock, enteritis, intestinal obstruction and neonatal lupus erythematosus.

Infants

All of above plus viral hepatitis A, B and C and ICC

Childhood and adolescence

- **Infections:** Hepatitis A, B, C, D and E, chronic hepatitis, liver abscess (both amebic and pyogenic), typhoid fever, malaria, hydatid cyst and infectious mononucleosis
- **Metabolic/Storage:** ICC, MPS, glycogen storage disease, lipidosis, alpha-1-antitrypsin deficiency and Wilson disease
- **Fatty Change/infiltration:** Kwashiorkor, Reye syndrome, tuberculosis, cystic fibrosis, nephritic syndrome, tetracycline toxicity
- **Malignancy:** Lymphomas, hepatoblastoma, histiocytosis, metastases
- **Congestive:** CCF, constrictive pericarditis, Budd-Chiari syndrome, VOD of liver
- **Miscellaneous:** Congenital cyst, drugs.

Abbreviations: CCF, congestive cardiac failure; VOD, veno-occlusive disease; ICC, Indian childhood cirrhosis; MPS, mucopolysaccharidosis; TPN, total parenteral nutrition; DNA, deoxyribonucleic acid.

Box 30.12 Liver span in different age groups

- **Infants:** 5–6.5 cm
- **1–5 years:** 6–7 cm
- **5–10 years:** 7–9 cm
- **10–15 years:** 8–10 cm.

- **Portal hypertension:** Noncirrhotic portal hypertension due to extrahepatic portal venous obstruction,* congenital hepatic fibrosis,* noncirrhotic portal fibrosis,* Budd-Chiari syndrome and cirrhosis.
- **Infections/immunological:** Malaria, (especially chronic malaria and tropical splenomegaly*), typhoid, kala-azar,* viral hepatitis, infectious mononucleosis, congenital infections (syphilis*).
- **Hematological malignancies:** Leukemias (especially chronic myeloid leukemia*), lymphomas (especially splenic lymphoma*), histiocytosis, myelin (proliferative disorder*).
- **Storage disorders/inborn errors of metabolism:** Gaucher disease*, Niemann-Pick disease and mucopolysaccharidosis (MPS).
- **Chronic hemolytic anemia:** Thalassemia*, sickle-cell anemia.

* All these conditions are associated with a massive splenomegaly.

Table 30.5: Helpful clues in evaluation of pediatric hepatomegaly

Parameter	Likely conditions
Sibling/familial involvement	ICC, Wilson disease, thalassemia
Transfusions/needle pricks	HBV, HCV
Fever	Enteric fever, malaria, viral hepatitis, leptospirosis (in acute cases), tuberculosis, kala-azar, chronic active hepatitis (in chronic cases)
Jaundice	Viral hepatitis, cirrhosis, enteric fever
Edematous PEM	Kwashiorkor
Anemia	Thalassemia, leukemia, portal hypertension
Lymphadenopathy	Hematogenous tuberculosis, malignancy
Engorged neck veins/raised JVP	Constrictive pericarditis
Rash	Histiocytosis
Cataracts with mental retardation and splenomegaly	Galactosemia
Hazy or cloudy cornea	Mucopolysaccharidosis type 1
Kayser-Fleischer ring	Wilson disease
Microcephaly/hydrocephalus	STORCH group of intrauterine infections
Neurological manifestations	Wilson disease
Refractory rickets	Cystinosis, tyrosinosis

Abbreviations: ICC, Indian childhood cirrhosis; HBV, hepatitis B virus; HCV, hepatitis C virus; STORCH syphilis; toxoplasmosis, other agent; rubella, cytomegalovirus and herpes simplex; PEM, protein energy malnutrition.

- **Extramedullary hematopoiesis:** Marble-bone disease (osteopetrosis*).

Table 30.5 gives the clues that are helpful in the differential diagnosis of hepatomegaly.

Investigations

Liver function tests, imaging studies and liver biopsy depending on the merit of the clinical scenario.

Treatment

It revolves around supportive and symptomatic care together with the attention to the etiological condition.

LIVER ABSCESS

Liver abscess(es) may be pyogenic, amebic or rarely, because of other causes (infected echinococcal cyst, Candida infection in immunocompromised subjects or neonates).

PYOGENIC LIVER ABSCESS**Etiology**

It is usually polymicrobial, the most common pathogen being *Staphylococcus aureus* in solitary abscess and

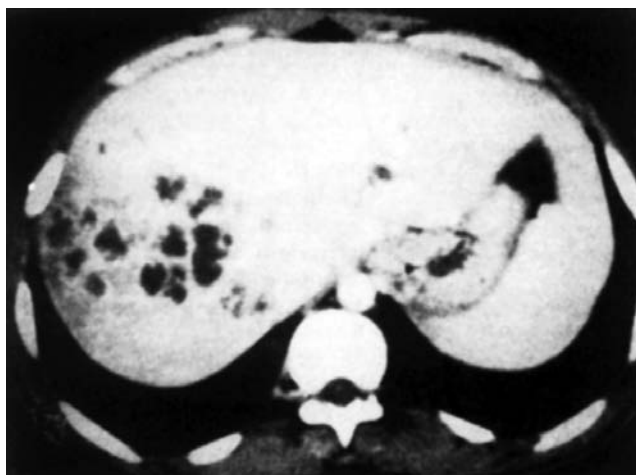


Fig. 30.8: Liver abscess. CT scan (contrast enhanced) showing multiple coalescent hypodense areas (right lobe of liver) consistent with pyogenic liver abscesses.

Gram-negative enteric bacilli and anaerobic organisms in multiple abscesses.

Predisposing factors include immunocompromised states (chronic granulomatous disease, acute lymphocytic leukemia {ALL}, steroid therapy, measles), malnutrition, bile duct ascariasis, skin infections, trauma, aplastic anemia and sickle-cell disease, ventriculoperitoneal shunt and in neonates, umbilical vessel catheterization, prematurity, suppurative umbilical thrombophlebitis, peritoneal abscess, skin infection, septicemia and surgical procedure for necrotizing enterocolitis (NEC).

Clinical Features

These include spiky pyrexia with chills and rigors, anorexia, nausea, vomiting, abdominal distention, right upper quadrant abdominal pain and lassitude. Examination may reveal, jaundice (in biliary tract obstruction), tender hepatomegaly or right upper abdominal mass.

Diagnosis

It is confirmed by imaging (Fig. 30.8).

Management

It consists of:

- Appropriate chemotherapy—a combination of penicillinase resistant penicillin (cloxacillin) plus an aminoglycoside or a third generation cephalosporin.
- Metronidazole for anaerobes.
- Percutaneous needle aspiration, catheter drainage and open surgical drainage.

Prognosis

Following prompt diagnosis and appropriate treatment, pyogenic abscess resolves in over 6 weeks.

Complications

These include pleuropulmonary involvement, peritonitis, subphrenic abscess, abscess-duodenum, fistula, hemobilia, pericardial effusion and Budd-Chiari syndrome.

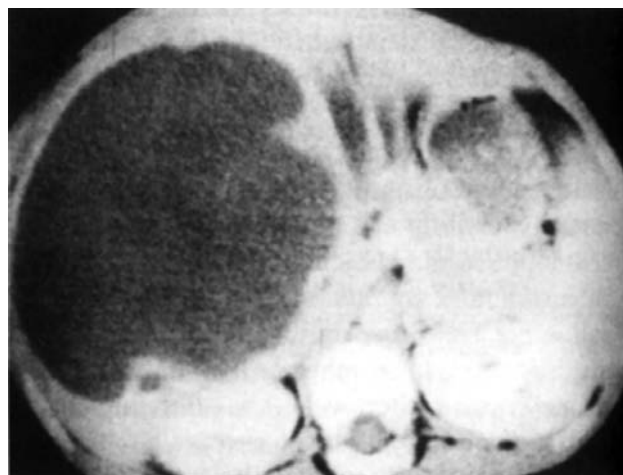


Fig. 30.9: Liver abscess. CT scan (contrast enhanced) showing a large hypodense area (right lobe of liver) consistent with a solitary amebic liver abscess.

AMEBIC LIVER ABSCESS

As already pointed out in Chapter 21 (Protozoal Infections and Infestations), it is extremely difficult to differentiate amebic liver abscess from pyogenic liver abscess on the basis of clinical presentations and imaging modalities (Fig. 30.9). The special investigations for this purpose include serology and liver aspiration under ultrasonography or CT scan.

Treatment is in the form of amebicidal drugs (parenteral metronidazole (20–50 mg/kg/day) for 7–10 days as such or in combination with tetracycline or chloroquine. In seriously sick cases, emetine hydrochloride, percutaneous needle aspiration, catheter drainage and open surgical drainage may need consideration.

THE CHILD WITH ASCITES

Definition

The term, *ascites*, refers to abnormal collection of fluid in the peritoneal cavity. As already described in Chapter 2 (Pediatric History-taking and Physical {Clinical} Examination), free fluid, in most instances, may be detected as shifting dullness with fluid thrill. It may be accompanied by pedal edema, scrotal edema or anasarca.

Etiology

Box 30.13 gives the list of causes of ascites according to age group.

Diagnostic Approach

Clinical Work-up

Good history and physical examination are of paramount importance. Most patients present with increasing abdominal distention (Fig 30.10), usually accompanied by weight gain. Box 30.14 lists the important features of three grades of ascites. In minimal ascites (at least 200 mL of fluid), one needs to elicit puddle sign (Lawson sign). Prominent collaterals in flanks and over back point to inferior vena cava obstruction. Prominent abdominal collaterals and caput medusae (Fig. 30.11) suggest ascites secondary to

Box 30.13 Etiology of pediatric ascites**Newborn**

- **Isolated:** Chylous (congenital anomalies of lymphatics), liver failure (hemochromatosis), idiopathic
- **With peritonitis:** Chemical (bile, meconium), bacterial
- **With hydrops:** Cardiovascular (hypoplastic left heart syndrome, Ebstein anomaly, heart block, auricular tachycardia), hematologic (chronic *in utero* anemia: homozygous alpha thalassemia, isoimmune hemolytic anemia), chromosomal (Trisomy 13, 18, 21, Turner syndrome), infections (STORCH), pulmonary (diaphragmatic hernia), renal (nephrosis, posterior urethral valve), maternal (diabetes mellitus, toxemias), placental (cord compression, chorangioma), storage, tumors (Wilms', neuroblastoma), skeletal (osteogenesis imperfecta, achondroplasia), hepatic (alpha-1-antitrypsin deficiency, hemochromatosis), idiopathic.

Infants and children

- **With portal hypertension:** Extrahepatic (splenic vein thrombosis, portal vein thrombosis, cavernous transformation, Budd-Chiari syndrome, inferior vena cava obstruction, CCF, A-V fistula), Intrahepatic (EHBA, choledochal cyst, hepatitis B and C, Wilson disease, alpha-1-antitrypsin deficiency, toxin-induced, cystic fibrosis, histiocytosis X, Schistosomiasis)
- **Without portal hypertension:** Tuberculosis, CCF, nephrotic syndrome

Acute ascites

- **Hepatic encephalopathy:** Acute/fulminant liver failure
- **Peritonitis:** Spontaneous perforation of bile duct
- **Venous obstruction** Budd-Chiari syndrome, portal vein thrombosis, inferior vena cava obstruction, splenic vein thrombosis, VOD.
- **Pseudoascites**
- **Massive intra-abdominal cyst:** Ovarian cyst, omental cyst and cystic lymphangioma.

Abbreviations: STORCH syphilis, toxoplasmosis, other agent, rubella, cytomegalovirus and herpes simplex; MPS, mucopolysaccharidosis; CCF, congenital cardiac failure; VOD, veno-occlusive disease, EHBA, extrahepatic biliary atresia.

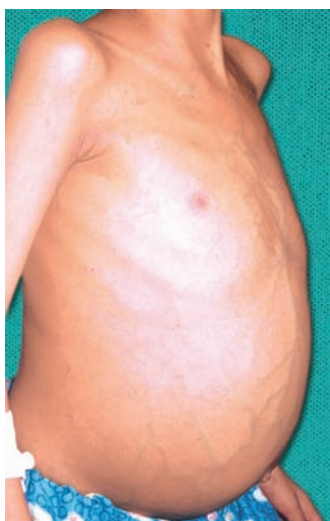


Fig. 30.10: Massive ascites: Note the massive abdominal distention with prominent thoracoabdominal venous network suggestive of liver disease.

Box 30.14 Grading of ascites

- **Mild/minimal (Grade I):** Positive puddle sign; fluid on ultrasonography (USG) abdomen
- **Moderate (Grade II):** Positive shifting dullness; negative fluid thrill
- **Severe (Grade III):** Positive fluid thrill; negative shifting dullness; respiratory distress.



Fig. 30.11: Caput medusa. Note the dilated veins spreading peripherally from umbilicus in a child with massive ascites secondary to cirrhosis.

liver disease. If jugular venous pressure (JVP) is raised, constrictive pericarditis is the most likely cause of ascites.

Special Investigations

- **Radiologic studies:** Ultrasonography is particularly of great value in detecting minimal ascites that may be missed by clinically. Infrequently, CAT scan and/or MRI may be required in difficult cases.
- **Upper gastrointestinal endoscopy** for detecting presence of esophageal or fundal varices.
- **Abdominal (ascitic/peritoneal) tap** for biochemistry and cytology of the ascitic fluid (Table 30.6). The procedure is described in Chapter 49 (Pediatric Practical Procedures)
- **Serum:** Serum ascites albumin gradient (SAAG) is of special importance (Box 30.15).

Some clinical clues to etiology of ascites are listed in Table 30.7.

Management

Treatment is dictated by the etiologic condition. Supportive treatment consists of sodium and fluid restriction, diuretics (potassium sparing aldosterone antagonists like spironolactone, loop like frusemide and combination of

Table 30.6: Characteristic features of ascitic fluid in major causes of ascites

Characteristics	Tuberculosis	Portal hypertension/ Cirrhosis	Pyogenic
Gross appearance	Clear	Straw-colored/ bile-stained	Turbid or purulent
Cell count	TLC >1000 Lymphocyte >70%	<250 Mesothelial 90%	>1000 PMN >50%
Protein	>2.5 g/dL	<2.5 g/dL	>2.5 g/dL
Specific gravity	>1.016	<1.016	>1.016

Footnote: Remarkable rise in amylase level in ascitic fluid (usually >2000 IU) supports pancreatitis or gut perforation whereas LDH elevation is of value in differentiating bacterial peritonitis from gut perforation.
Abbreviations: TLC, total leukocyte count; PMN, polymorphonuclear leukocyte.

Box 30.15 Interpretation of SAAG gradient**SAAG <1.1 g/dL (low gradient)**

- **Significance:** Absence of portal hypertension.
- **Conditions:** Tuberculosis, nephritic syndrome, biliary leak, serositis, peritoneal carcinomatosis

SAAG >1.1 g/dL (high gradient)

- **Significance:** Portal hypertension
- **Conditions:** Cirrhosis, acute/fulminant liver failure, portal vein thrombosis, Budd-Chiari syndrome.

Abbreviation: SAAG, serum albumin-ascites gradient.

Table 30.7: Some clues to etiologic comorbid conditions in ascites

Clue	Condition
Monomicrobial infection	Spontaneous bacterial peritonitis
Polymicrobial infection	Intestinal perforation
High concentration of urea and creatinine in ascitic fluid	Uroascitis
High ascitic bilirubin	Biliary tree/upper intestinal perforation
Milk-like ascitic fluid due to high Concentration of triglycerides (Chylous ascites)	Tuberculous abdomen
High SAAG gradient	Portal hypertension
High ascitic fluid amylase	Pancreatitis

Abbreviation: SAAG, Serum ascites albumin gradient.

the two types) and beta-blockers (propranolol). Refractory ascites may be offered the benefit of a:

- Large volume (upto 100 mL) tap
- Colloidal replacement with dextran or albumin
- Transjugular intrahepatic post-canal shunt (TIPS)
- Liver transplantation.

INDIAN CHILDHOOD CIRRHOSIS**(Infantile Cirrhosis, Infantile Biliary Cirrhosis, Hypertrophic Biliary Cirrhosis, Subacute Toxic Cirrhosis)**

Cirrhosis may result from various diseases such as atresia of bile duct, neonatal hepatitis, cystic fibrosis, hepatolenticular degeneration, galactosemia, glycogen storage disease, syphilis or schistosomiasis.

Indian childhood cirrhosis is a disease peculiar to the Indian infants and children, usually 6 months–4 years of age. It was first described by Sen in 1887 from Calcutta. The remarkable decline in ICC incidence appears to be related to declining practice of employing copper/brass utensils for boiling milk.

Etiologic Considerations

Over the decades, hypotheses such as ‘nutritional’, ‘viral’, ‘hepatotoxic’ ‘genetic’, ‘metabolic’ and ‘autoimmune’ have been postulated. No single factor seems to be the cause of ICC. It is possible that a genetically-prone child suffers from one or more of the superadded factors (viral, toxic, metabolic and/or autoimmune), leading to the overt picture of ICC.

Many-fold increase in liver copper in ICC may be related to early introduction of feeds contaminated with copper from copper and/or brass utensils. Detailed analysis of feeding histories of ICC cases has established that the source of copper in them is top milk (started quite early in infancy), boiled or stored in brass vessels.

Pathology

The basic pathologic change is the diffuse liver cell damage by way of degeneration going on to necrosis and replacement fibrosis. In an established case, there is combination of degenerative changes in hepatocytes, scattered fibrosis, electron lucent cytoplasmic areas with loose arrangement of organelles, indistinct outline of mitochondria, fine fibrillar Mallory hyaline and irregular dense bodies (cuprosomes).

Similar histopathology is seen in a newly-identified disorder, **hepatic copper overload syndrome**, in American children. This form of cirrhosis has a genetic disturbance in copper metabolism as in Wilson disease. However, onset is early and the affected children die before the age of 6 years or so.

Clinical Features

Acute-onset ICC is infrequent and sometime mimics VOD (Table 30.8). It presents with jaundice, fever, clay-colored stools and hepatomegaly. Rapid downhill course finally terminates in death. Insidious onset ICC shows three arbitrary stages which tend to merge with each other.

1. **Stage I** is characterized by enlarged firm liver with sharp leafy border.
2. **Stage II** is marked by further enlargement of liver, jaundice and portal hypertension (Fig. 30.12).
3. **In stage III** (terminal stage) manifestations of hepatocellular failure supervene.

Diagnosis

Liver biopsy is the only reliable method of arriving at a foolproof diagnosis. However, it may not be feasible in an advanced ICC when prothrombin time is prolonged.

Treatment

Indian childhood cirrhosis, once dubbed as a **frustrating situation** for which no specific treatment was available, may respond to D-penicillamine when therapy is initiated at an early stage (before the development of jaundice or ascites).

Table 30.8: ICC and VOD

Factor	ICC	VOD
Onset	Generally insidious	Always acute
Etiology	Not known copper overload	Hepatotoxic component of bush tea
Presence of veno-occlusive element	Not seen in most cases	Outstanding feature

Abbreviations: ICC, Indian childhood cirrhosis; VOD, veno-occlusive disorder.



Fig. 30.12: Indian childhood cirrhosis (ICC). The child presented with definite jaundice, hepatosplenomegaly, ascites, edema, anemia and growth failure. Liver biopsy confirmed the clinical impression.

Table 30.9: Strategy of preventing ICC through lowering of the copper intake

Source of high dietary copper	Action plan to lower it
Brass and copper vessels for transportation, storage and boiling of milk	Use of aluminum and steel for tin-coating on brass
Copper and brass pots for storing drinking water	Change-over to earthenware or steel and aluminium
Food cooked and stored in brass and copper utensils	Encourage use of aluminium and steel
Introduction of animal milk before 2–3 months of age	Promotion of breastfeeding
Copper content of drinking water under 0.1 mg/L	Demineralize water
Foods rich in copper content (liver, nuts, chocolates)	Avoid them or minimize their consumptions

Prognosis

Despite the best of efforts, ICC invariably had a fatal outcome in the past.

Prevention (Table 30.9)

Etiological role of copper has received considerable support from the fact that avoidance of brass and copper vessels for infant feeding with prolonged breastfeeding and cereal supplementation has virtually eliminated ICC.

REYE SYNDROME

(White Liver Disease, Encephalopathy with Fatty Degeneration of the Viscera)

Reye syndrome, earlier reported by Khan from India in 1956 under the semantic *Jamshedpur fever*, was first described from Australia by Reye and coworkers in 1963.

Definition

Reye syndrome is characterized by encephalopathy and fatty infiltration of liver and other viscera, especially kidney and cerebral edema with diffuse mitochondrial injury.

Epidemiology

It has been reported from almost all over the world. There are instances of familial occurrence. The usual age group suffering from the syndrome is 3 months to 18 years. There are occasional reports of its occurrence in neonates and adults. The sex incidence is equal. The syndrome has been reported in twins, siblings and offspring's of first-cousin marriages.

Etiopathogenesis

The exact etiology continues to be unclear. The most noteworthy observation is that a strong epidemiologic connection of Reye syndrome with prior administration of aspirin in children suffering from viral illnesses like influenza B or chickenpox stands established.

Just like the drug (aspirin), toxins (aflatoxin), viral infections (varicella, influenza) and some inborn errors of metabolism (single enzyme defects of beta-oxidation) have been shown to precipitate this syndrome. In nutshell, Reye syndrome appears to be a stereotyped reversible reaction in mitochondria arising from an interaction of viral, toxic and host-genetic factors.

Central nervous system manifestations appear to be secondary to metabolic effects of hepatic dysfunction rather than primary CNS infection. Hypoglycemia, hyperammonemia and increased levels of fatty acids—acting singly or in combination may be important contributory factors. It has been suggested that inhibition of fatty acid oxidation in the endothelial cerebral edema underlies the development of cerebral edema. Defective oxidative phosphorylation within the cells may interfere with the transport of glucose from blood to brain.

Pathology

- The pathologic features of the disease are well defined.
- Cerebral edema (without cellular infiltration or demyelination), brainstem herniation and enlarged fatty liver (panlobular microvesicular fat accumulation) without any necrosis are invariably present.
- Anoxic neuronal degeneration may or may not be present.
- Identical changes are found in the kidney minus glomeruli, blood vessels and interstitial tissue.
- Distinctive pathologic features (seen only on electron microscopy) include enlarged pleomorphic mitochondria with fragmented cristae and flocculation of intramitochondrial protein. Markedly reduced activity of all mitochondrial enzymes in first 26 days of disease may be demonstrated.

Clinical Features

Clinical spectrum ranges from relatively mild to rapidly fatal. It is more severe in infants than in latter age group.

Box 30.16 Clinical staging of Reye syndrome

- **Grade 1:** Somewhat confused, lethargic and sleepy; vomiting, anorexia
- **Grade 2:** Delirious, very lethargic, confused; hyperventilation; hyperreflexia.
- **Grade 3:** Comatose (light) with or without convulsions; decorticate rigidity; pupillary light reaction intact.
- **Grade 4:** Deepening coma, convulsions, decerebrate rigidity, oculoccephalic reflexes lost, pupils fixed.
- **Grade 5:** Deep coma, deep tendon reflexes lost, respiratory arrest, pupils fixed and dilated, intermittent flaccidity or decerebrate rigidity; isoelectric electroencephalogram (EEG).

■ **Manifestations in infants:**

- Dyspnea, hyperventilation, convulsions, apnea, hepatomegaly and features of hypoglycemia.
- Death rate is much more than in older children.
- Survivors show greater incidence of neurological sequelae.

■ **Manifestations in children and adolescents:**

- The syndrome manifests 3–4 days after the onset of a mild prodromal viral illness like upper respiratory infection (URI), exanthemata (say chickenpox) or diarrhea.
- In a typical case, there is a sudden onset of profound disturbances of sensorium (to the extent of coma), vomiting and convulsions.
- There are no focal neurologic signs of meningeal irritation.
- Hypoglycemia, hepatomegaly and hepatic dysfunction are the other prominent manifestations.
- Jaundice is, as a rule, conspicuous by its absence.
- Electrolyte imbalance or bleeding diathesis may accompany.

Mild cases may be missed without liver biopsy. Box 30.16 gives staging of Reye syndrome.

Complications

- Pneumonitis
- Respiratory failure
- Cerebral problems
- Cardiac arrhythmias
- Diabetes insipidus.

Differential Diagnosis

Clinical picture simulating Reye syndrome may be encountered in:

- CNS infections or intoxications: encephalitis, meningitis, toxic encephalopathy
- Hemorrhagic shock with encephalopathy
- **Toxins:** Hypoglycin A, valproate
- Drug ingestion, e.g. salicylate, valproate
- **Metabolic diseases:** Fructosemia, systemic or hepatic carnitine deficiency, organic acidurias.

Laboratory Diagnosis

- Blood and CSF sugar are usually low.
- Blood ammonia is elevated in most cases.

- Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT) and LDH are significantly elevated.
- Serum bilirubin and alkaline phosphatase are either normal or only slightly raised.
- Prothrombin time is prolonged.
- Blood urea nitrogen is elevated in few cases.
- Metabolic acidosis and respiratory alkalosis may coexist in the same patient.
- Liver biopsy shows diffuse microvesicular steatosis with absence of glycogen and slightest inflammatory changes.
- EEG changes consist of predominantly of slow wave activity.

Treatment**Specific Measures**

Since the etiology is at best speculative, treatment is simply empirical.

- Restoration of blood glucose level is by 10–25% glucose IV.
- Correction of electrolyte imbalance.
- Control of seizures should be achieved.
- Cerebral edema may be minimized with 20% mannitol infusion, 0.5 g/kg ever 6 hourly, and/or corticosteroids (dexamethasone).
- Double volume exchange transfusion and peritoneal dialysis may prove of value in correcting metabolic defects, such as elevated blood ammonia level as well as blood dyscrasias, if present.
- Vitamin K.
- Fresh frozen plasma.

Diet

- In view of hepatic failure, a diet low in proteins with sufficient carbohydrates for calories (energy) reduces exogenous protein catabolism. Neomycin by nasogastric tube and enema—as used in hepatic coma—is also a useful measure.
- L-carnitine, if used at an early stage, may be of value in safeguarding from progression of clinical Reye syndrome or Reye-like syndrome.

Surgery

In desperate situations, surgical decompression of raised intracranial pressure (RIP) may be warranted as a life-saving resort.

Prognosis

A majority of the children (>50%) suffering from Reye syndrome die while in deep coma, often within first 24 hours of the onset of neurological manifestations. Overall mortality may be as high as 85%. Recently, low death rate (20–30%) has been reported. Most patients die of CNS complications. Factors that indicate poor prognosis early in the course of the disease are listed in Box 30.17.

Box 30.17 Indices of poor prognosis in Reye syndrome**Stage 1: Encephalopathy**

- Blood ammonia over twice the upper limit of normal.
- Prothrombin time over 3 seconds.

Stage 2–4: Encephalopathy

- Age under 1 year
- Rapid progression of symptoms to stage 4 encephalopathy
- Ammonia over 6 times the normal
- Creatine phosphokinase over 10 times the normal
- SGOT/SGPT ratio less than 1
- EEG showing marked slowing
- Nonesterified fatty acids greater than 71 mEq/L
- Marked elevation in long-chain dicarboxylic acids

Most survivors generally recover completely. Neurological sequelae such as mental retardation, epilepsy, hydrocephalus, behavioral problems, spasticity and hemiplegia may occur in others. Recurrences have also been recorded though only infrequently.

Abbreviations: SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; EEG, encephalography.

Box 30.18 Major indications of liver transplantation

- **Fulminant liver failure:** Viral, drug-induced, autoimmune, toxin-induced, perinatal hemochromatosis, Wilson disease, tyrosinemia, idiopathic.
- **End-stage liver failure:**
 - **Obstructive biliary tract disease:** EHBA, sclerosing cholangitis, postsurgical biliary tract diseases.
 - **Intrahepatic cholestasis:** Syndromic bile duct paucity (Alger syndrome), nonsyndromal bile duct paucity, intrahepatic cholestasis, idiopathic neonatal hepatitis.
 - **Chronic active hepatitis/cirrhosis:** Hepatitis B, C, autoimmune, idiopathic.
 - **Metabolic disorders:** Alpha-1-antitrypsin deficiency, Wilson disease, tyrosinemia type 1, glycogen-storage disease (type 1, 3, 4), cystic fibrosis.
 - **Miscellaneous:** Cryptogenic cirrhosis, congenital hepatic fibrosis, TPN-associated cirrhosis.
- **Metabolic disorders:** Crigler-Najjar (type 1) primary leading to hepatic disease, oxalosis, familial cholesterolemia, urea cycle defects, organic acidemias.
- **Unresectable liver:** Hepatoblastoma, hepatocellular carcinoma, hemangioendothelioma, hemangiomas.

Abbreviations: EHBA, extrahepatic biliary atresia; TPN, total parenteral nutrition.

LIVER TRANSPLANTATION**Indications**

Liver transplantation has revolutionized the treatment of ESLD, acute liver failure and metabolic liver disease. Box 30.18 lists important indications of liver transplantation.

Contraindications

- **Absolute**
 - Incurable extrahepatic malignancy
 - Sepsis
 - Incurable extrahepatic disease.
- **Relative**
 - Malignancy considered to be cured or curable
 - Sepsis which is treatable
 - Human immunodeficiency virus (HIV)
 - Progressive extrahepatic disease
 - Substance abuse.

Procedure

Figure 31.13 presents highlights of the surgical procedure.

Complications

These include septicemia, vascular thrombosis, biliary complications, poor graft function, chronic rejection, renal failure, hypertension, intestinal perforation and hematemesis (Fig. 30.14).

Immunosuppression to Prevent “Rejection”

In order to reduce the frequency of allograft rejection, it is a usual practice to give triple immunosuppression with prednisolone, azathioprine and cyclosporine post-operatively. In case of rejection, pulse prednisolone therapy (10 mg/kg/day is given for 3 days). In the event of steroid resistance or cyclosporine-induced renal dysfunction, newer immunosuppressants such as tacrolimus may be employed.

Results

Currently, 1 year and 5 year survival rates are 90% and 80%, respectively. First successful liver transplant done at Apollo Hospital, New Delhi, has completed its 14 years.

PANCREAS: BASICS IN A NUTSHELL

Pancreas, a retroperitoneal organ, is positioned posterior to the stomach and lesser sac and anterior to the abdominal aorta and upper lumbar vertebrae. The head is nestled in the duodenal cap whereas the neck, body and tail extend obliquely and superiorly so that tail comes close to the splenic hilum. The common bile duct extends inferiorly through or behind the pancreatic head-on way to duodenum.

All through the length of pancreas runs the so-called **duct of Wirsung** that drains the pancreatic exocrine secretions and enzymes into the duodenum.

Pancreatitis is an inflammation of the pancreas with a multitude of triggers that cause activation of proteases within the gland. Three types of pancreatitis are:

1. **Acute pancreatitis**, which may be mild or severe, but is potentially reversible.
2. **Chronic pancreatitis**, which is characterized by permanent morphological changes.
3. **Recurrent pancreatitis** usually hereditary, predisposes to cancer of pancreas.

ACUTE PANCREATITIS

Acute pancreatitis is quite infrequent in childhood. When, it occurs, it is a less severe disease than in adults.

Etiology

Common causes of acute pancreatitis in children include:

- **Infections:** Usually viral infections, say mumps
- Abdominal injury
- Systemic diseases
- **Drugs:** Sodium valproate, L-asparaginase
- **Congenital defects:** Choledochal cyst
- **Metabolic:** Hypertriglyceridemia, hypercalcemia
- **Collagenosis:** Henoch-Schonlein purpura

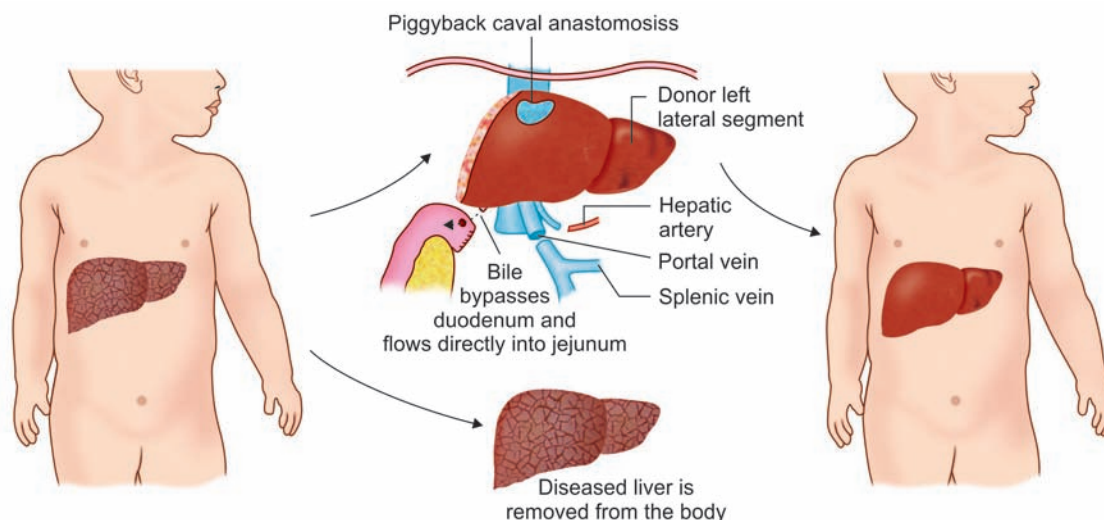


Fig. 30.13: Liver transplantation. Pictorial representation of the highlights of the surgical procedure.

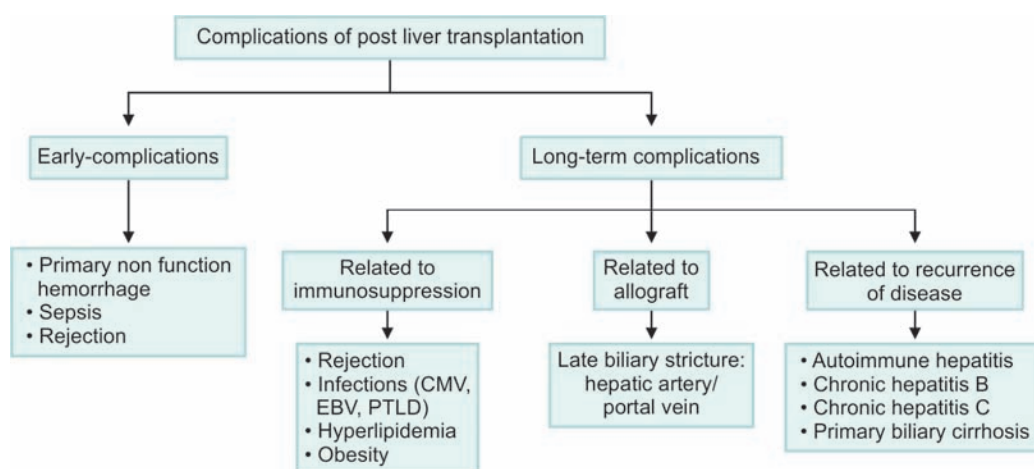


Fig. 30.14: Complications of post liver transplantation.

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; PTLD, post transplant lymphoproliferative disorder.

- Gallstones
- Idiopathic.

Clinical Features

Only 20% cases are with severe pancreatitis. Rest has mild illness. Mild cases have only pancreatic interstitial edema and no complications. Severe cases suffer from pancreatic necrosis and complications (Box 30.19). Manifestations include upper abdominal pain in some cases radiating to back, nausea vomiting and anorexia.

Complications

Both local and remote complications can occur in acute pancreatitis (Box 30.19).

Pathophysiology

Inflammatory involvement of pancreas triggers activation of trypsinogen to active trypsin. Trypsin activates proenzymes and precursors of elastase, carboxypeptidase and phospholipase A. This leads to complications—both local and systemic. Without treatment, sepsis and multiorgan failure syndrome may follow with serious outcome.

Box 30.19 Complications of acute pancreatitis

Local

- Necrosis
- Pseudocyst
- Abscess
- Hemorrhage
- Fluid collection.

Systemic

- Gastrointestinal bleed
- Intestinal obstruction
- Intestinal perforation
- Vascular aneurysms
- Splenic infarction
- Acute respiratory distress syndrome (ARDS)
- Pleural effusion
- Pericardial effusion
- Myocardial depression
- Shock
- Disseminated intravascular coagulation
- Hyperglycemias
- Hypocalcaemia
- Acute tubular necrosis with acute renal injury.

610 **Diagnosis****Clinical**

Clinical presentation with acute upper abdominal pain, nausea, vomiting and abdominal distention must arouse suspicion. In the absence of bowel sounds, tachycardia, low BP and cutaneous bleeds, the disease is likely to be severe. Obese adolescent stands enhanced risk of more severe disease.

Investigations

- Serum amylase and or serum lipase levels more than 3 times higher than upper range of normal.
- Plain X-ray of chest and abdomen for pleural effusion, ileus (local or generalized) and colon cutoff sign.
- Ultrasonography for:
 - Diffuse enlargement of pancreas and decrease in pancreatic echotexture compared to the left lobe of the liver.
 - Structural pancreatic-biliary abnormalities, e.g. choledochal cyst, gallstones, dilatation of pancreatic biliary tree.
- CT scan may be required in difficult cases.
- Contrast enhanced CT (CECT) is excellent for detecting parenchymal necrosis.
- MRI too can be employed. Though somewhat less sensitive than CECT, its advantage lies in avoiding radiation.

Hematological and Serum Markers for Predicting Severity?

- C-reactive protein (CRP) (>150 mg/dL) at 48 hours
- High hematocrit (>40) is predictive of a severe attack
- Tumor necrosis factor (TNF)

- IL 1, 6 and 8
- Procalcitonin
- High polymorpholeukocyte elastase.

Treatment

Acute severe pancreatitis is an emergency.

■ **Medical**

- Resuscitation and rehydration
- Oxygen
- Nasogastric tube placement
- Analgesics
- Nutrition
- Antibiotics

Prompt relief of pain is important in pancreatitis. Hence powerful analgesics such as morphine meperidine or fentanyl need to be used.

- **Pancreatic stenting:** In traumatic pancreatitis and pancreatitis with pseudocyst pancreatic, stenting may be warranted.

- **Endotherapy:** In acute gallstone pancreatitis, endotherapy may be needed.

- **Surgery:** Indications are:

- Choledochal cyst
- Gallstones
- Pseudocyst
- Pancreatic abscess
- Infected necrosis.

Prognosis

Recurrence occurs when the etiologic condition is left untreated. It is, therefore, mandatory that condition predisposing to the attack is identified and treated.

Multiple Choice Questions

1. Spot the wrong observation:
 - A. Conjugated bilirubin forms 15–20% of total serum bilirubin
 - B. Indian childhood cirrhosis has become rare after the practice of using brass vessels for boiling milk went out of favor
 - C. Encephalopathy, hypoglycemia and hepatomegaly without jaundice is classical for Reye syndrome
 - D. Incubation period of viral hepatitis A is around 15–50 days and of hepatitis B is 50–150 days
 - E. Straw-colored ascitic fluid suggests tuberculous abdomen
2. Which one of the wrong statements is about neonatal cholestasis syndrome:
 - A. Prolonged elevation of serum levels of conjugated bilirubin beyond 14 days of life
 - B. Choledochal cyst is a surgically correctable cause
 - C. Cherry red spots point to galactosemia
 - D. Liver transplantation is indicated in end-stage liver disease
 - E. Choreoretinitis points to an intrauterine infection (rubella, toxoplasmosis or cytomegalovirus)
3. Spot the wrong observation about extrahepatic portal hypertension:
 - A. Umbilical sepsis during neonatal period, umbilical vein catheterization and dehydration are its common causes
 - B. Ascites never shows fluctuation in this condition
 - C. Splenomegaly with or without hepatomegaly is the most consistent finding
 - D. Ultrasonography is an excellent modality for defining the site of obstruction
 - E. Portocaval anastomosis is the best procedure provided that portal vein is not obstructed
4. A sharp leafy liver border is a feature of:
 - A. Fulminant hepatitis
 - B. Indian childhood cirrhosis
 - C. Neonatal hepatitis
 - D. Glycogen storage disease
 - E. Wilson disease

contd...

5. Spot the correct statement:

- A. Portal hypertension exists when pressure in portal venous system is greater than 12 mmHg
- B. Budd-Chiari syndrome is common in children
- C. Protein greater than 2.5 g/dL in ascetic fluid suggests diagnosis of cirrhosis
- D. In tuberculous ascitic fluid, appearance is turbid
- E. Acute acalculus cholecystitis is almost always due to Kawasaki disease

Answers

1. E 2. C 3. B 4. B 5. A

Clinical Problem-solving

Review 1

A 9-year-old girl presents with anorexia, nausea, vomiting, abdominal discomfort, fever and yellow urine. No history of intake of any drugs in the recent days. Liver enlarged (span of 11 cm) and tender; spleen just palpable.

1. What is your provisional clinical impression?
2. How do you justify your diagnosis in the absence of jaundice?
3. Which commonly employed drug(s) should be avoided in this case?

Review 2

An otherwise healthy adolescent, aged 15 years, presents with sudden onset of spiky fever with chills and rigors and right upper abdominal pain. Examination shows a toxic-looking child with a tender lump in continuity with somewhat enlarged liver. There is no jaundice and no splenomegaly.

1. What is the most likely diagnosis?
2. Name an investigation that will confirm your clinical diagnosis.
3. What is the recommended therapeutic approach?

Answers**Review 1**

1. The clinical profile is consistent with the diagnosis of viral hepatitis A.
2. Jaundice in viral hepatitis A makes its appearance later, usually when the initial symptoms have regressed.
3. Hepatotoxic drugs like paracetamol and chlorpromazine should be avoided in a case of viral hepatitis A.

Review 2

1. Liver abscess, in all probability pyogenic.
2. Imaging (X-ray, ultrasonography, CT scan, radionuclide scans). It is advisable to culture the aspirate both aerobically and anaerobically.
3. In addition to drainage and appropriate antibiotics (penicillinase-resistant penicillin plus aminoglycoside, third generation cephalosporins), it is advisable to add metronidazole to cover anaerobic pathogens.

FURTHER READING

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BASICS OF THE RENAL SYSTEM

The kidney develops as a penetration of meta-nephros by ureteric bud, an outgrowth of mesonephric duct during 5th week of gestation. By 36 weeks, full number of nephrons have developed, though the functional maturity continues well after birth, usually until 2 years of age.

Nephron, the basic structural and functional unit, consists of a glomerulus and a long renal tubule consisting of proximal and distal convoluted tubules and collecting ducts (Fig 31.1). Each kidney contains approximately one million nephrons. The proximal convoluted tubule reabsorbs about 65%, the loop of Henle 15%, the distal convoluted tubule 10% and collecting ducts 9% of the glomerular filtrate. Thus, only 1% of filtrate is excreted in urine. **Capillary wall** is made of fenestrated endothelium, basement membrane and podocytes (foot processes) of visceral epithelial cells. **Basement membrane** is made of collagen, lamina and heparin sulfate proteoglycan.

The so-called **Bowman space** drains into proximal tube that leads into loop of Henle and distal tubule. Around 7 distal tubules join to form the collecting ducts that finally open into the renal pelvis. In order to stabilize plasma bicarbonate at 26–28 mEq/L, the filtered bicarbonate is mostly reabsorbed in the proximal convoluted tubules. Major urinary acidification is done through ammonia excretion and titratable acid. Urinary concentration is maintained at 280–290 mOsm/kg. In this endeavor, anti-diuretic hormone (ADH) plays an important role. It acts on collecting ducts, thereby facilitating passage of water from lumen to hyperosmotic interstitium.

As blood passes through glomerular capillaries, plasma is filtered. The cell-free ultrafiltrate contains all substances in

plasma, i.e. electrolytes, glucose, phosphate, urea, creatinine, peptides, low molecular weight proteins except proteins having a high molecular weight (>68000). Glomerular filtration is the net result of opposing forces across the capillary wall, namely the force for ultrafiltration, glomerular capillary hydrostatic pressure and the force opposing ultrafiltration, glomerular capillary oncotic pressure.

In case of a newborn, function is insufficient as compared to grown-up children or adults. Glomerular filtration rate (GFR) at birth is as low as 10–20 ml/min/1.73 m². It rises to 75–80 ml/min/1.73 m² by 6 weeks. High serum creatinine at birth falls to 0.4 mg/dL by 7th day of life. Sodium and bicarbonate reabsorption and hydrogen ion excretion are limited. As a result, the newborn's pH of urine is far higher than the magnitude of acidemia. Renal function continues to improve until it approaches adult level by end of 2 years.

DIAGNOSTIC WORK-UP FOR RENAL DISORDERS

CLINICAL EVALUATION

A good history and clinical examination are mandatory for diagnostic work-up of a renal disease. Clinical features of renal disease such as change in micturition habit, edema, hematuria, oliguria/anuria and dysuria, pain in flanks, ureteric colic, enuresis, growth retardation, anemia and abdominal lump should be kept in mind. Remember, a serious renal disorder may linger on without any overt manifestations.

Common problems of neonatal period are congenital malformations. In age group, from infancy to 3 years, urinary tract infection (UTI), Wilms' tumor, multicystic renal dysplasia, hemolytic uremic syndrome (HUS), nephrotic syndrome, renal tubular acidosis and Fanconi syndrome are seen. In 3–6 years group, nephrotic syndrome (NS), acute nephritis, rickets (usually secondary) and HUS are relatively frequent. Beyond 6 years (including adolescence), common problems are acute nephritis, NS (usually nonminimal variety), chronic renal failure, symptomatic hypertension and systemic lupus erythematosus (SLE).

INVESTIGATIVE EVALUATION

- **Urinalysis**, an important part of investigative evaluation, involving appropriate collection and tests for protein and glucose plus microscopy, is described in details See Chapter 50 (Pediatric Laboratory Procedures).
- **Blood levels of creatinine** (normal to <6 years 0.2–0.5 mg%, >6 years: 0.4–0.8 mg%) and **urea** (normal: 20–40 mg%); pH, bicarbonate, electrolyte and osmolality in tubular dis-

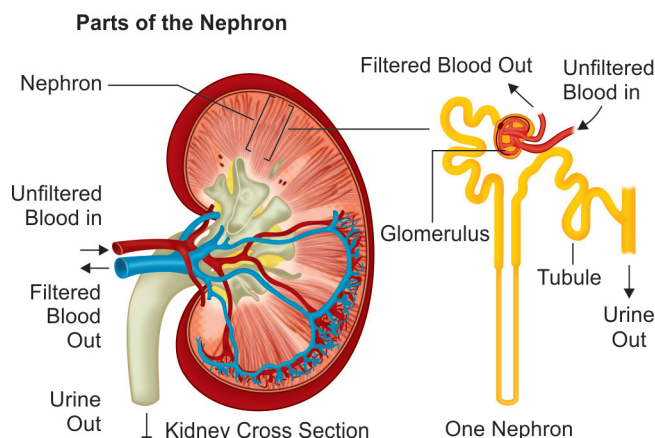


Fig. 31.1: Nephron: Note the details in the cross-section of the kidney.

orders and renal failure. Serum albumin, cholesterol, antistreptolysin O (ASO) titer, complement level, immunoglobulins and autoantibodies depending on merits of the case.

- **Glomerular filtration rate** is measured by creatinine clearance. Its normal value varies between (100 and 125 ml/minute/1.73 m²). GFR is, however, best measured by inulin clearance which is a cumbersome technique. Radionuclide clearance is yet another method of accurately computing GFR.
- **Urine concentration test** following fluid deprivation and measuring urine osmolality or administering desamino-8-D-arginine vasopressin (DDAVP) nasally or intramuscular (IM) injection and measuring urine osmolality.
- **Imaging of urinary tract** by plain X-ray, intravenous pyelogram (IVP), ultrasonography (USG), micturating cystourethrogram (MCU), radionuclide imaging, etc.

CONGENITAL MALFORMATIONS OF KIDNEY AND URINARY TRACT

Congenital defects of urinary tract are found in about 8%–10% of children, majority of them producing no significant problem. Yet, approximately one-fourth of pediatric chronic renal failure is secondary to such malformations. These are outlined in Box 31.1. Clinical clues for developmental anomalies of kidney and urinary tract include low-set/malformed ears, Potter facies, oligohydramnios, fetal compression syndrome, Trisomies 13 and 18, tuberous sclerosis, Wilms' tumor, meningomyelocele, sacral anomalies, spinal and lower limb defects, imperforate anus, genital anomalies, cystic disease of liver, hepatic fibrosis, single umbilical artery and family history of renal disease.

RENAL AGENESIS

Bilateral renal agenesis is not compatible with postnatal life, the stillborn showing stigmata of prenatal renal failure and oligohydramnios in the form of characteristic Potter facies (widely-separated eyes with epicanthal folds, broad and flat nose, small and receding chin and lowset ears) and limb malformations. Associated anorectal, cardiovascular and skeletal anomalies are common.

Unilateral renal agenesis must be excluded in neonates with single umbilical artery. It is usually accompanied by enlargement (compensatory) of the contralateral kidney, and anomalies such as involving the genitourinary tract (40%), skeletal system (30%), cardiovascular system (CVS) and gastrointestinal tract (GIT) (15%), central nervous system (CNS) and respiratory system (10%). When it is accompanied by vaginal agenesis or atresia, the combination is termed as **Mayer-Rokitansky syndrome**.

Box 31.1

Congenital malformations of kidney and urinary tract

- **Kidney:** Renal agenesis, horse-shoe kidney, polycystic disease of kidneys, duplex renal system, pelviureteric function stenosis.
- **Bladder and urethra:** Ectopia vesicae, patent urachus, bladder-neck obstruction, posterior urethral valves, neurogenic bladder, hypospadias, phimosis, structural defects of meatus or urethra.

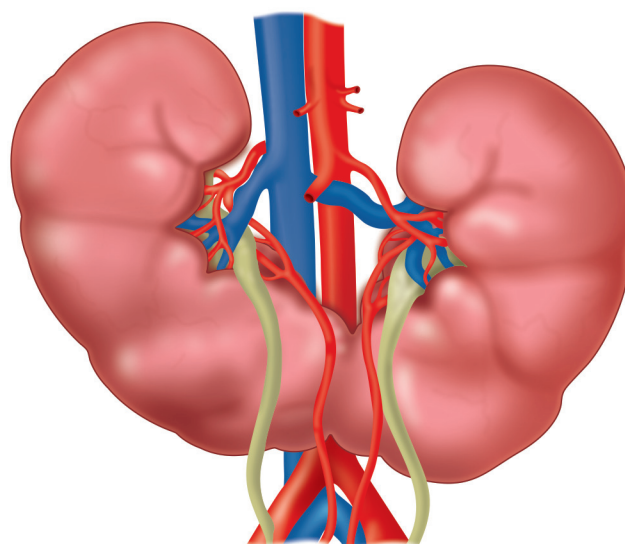


Fig. 31.2: Horse-shoe kidneys. Note the lower poles of the independently functioning kidneys connected with each other. Vulnerability to develop Wilms tumor is several times more in these children.

HORSE-SHOE KIDNEYS

When lower poles of the kidneys are fused in the midline, the condition is called **horse-shoe kidneys** (Fig 31.2). The incidence is remarkably high in Turner syndrome—7% against 1:500 in random births. Such kidneys are 2–8 times more vulnerable to develop Wilms' tumor than in general population.

POLYCYSTIC DISEASE OF KIDNEYS

It is of two types:

1. **Infantile type:** It is inherited as an autosomal recessive disease. The renal tissue is full of multiple small cysts and the organ is palpable as large spongy kidney of the newborn. Polycystic disease is often present in liver, lungs and pancreas. Hypertension, congestive cardiac failure (CCF) and uremia usually prove fatal in early infancy.
2. **Adult type:** It is inherited as an autosomal dominant disease. Multiple cysts are present in both kidneys. Decrease in renal function may not manifest before the age of 40 years.

DUPLEX RENAL SYSTEM

The term refers to a kidney with double pyelocalyceal systems with single, bifid, or two ureters.

PELVIURETERIC JUNCTION (PUJ) STENOSIS

It may be unilateral or bilateral, presenting as a flank lump without any symptoms or with UTI and upper abdominal pain.

POSTERIOR URETHRAL VALVES

These may present as recurrent UTI, dribbling, abnormal urinary stream, palpable bladder and renal dysplasia. Diagnosis is clinched by MCU which shows dilated posterior urethra, valves at the point of its junction with anterior urethra, enlarged bladder with vesicoureteric reflux (VUR).

614 MEATAL STENOSIS

Rarely, considerable stenosis of urethral meatus may cause urinary tract obstruction. Meatal dilatation or meatoplasty relieves the obstruction.

PHIMOSIS AND PARAPHIMOSIS

Phimosis is the inability to retract the prepuce after the age of 3 years. The prepuce is usually unretractable at birth. In 90% cases, it becomes retractable by the age of 3 years. By adolescence, only 1% boys have phimosis.

Phimosis may be congenital or secondary to inflammatory condition(s) of the glans or prepuce. Standard treatment is circumcision. Alternatively, betamethasone cream may be applied to the narrowed preputial skin twice daily for 4 weeks. After 2 weeks, the foreskin becomes soft and elastic and is retracted gently and gradually in increments. In a vast majority of the cases, the treatment proves successful.

Paraphimosis means that once the prepuce (phimotic) is retracted behind coronal sulcus, it cannot be reduced, causing venous stasis and edema with severe pain. Advanced cases need circumcision. In others, reduction can be attained by application of lubricants under cover of heavy sedation.

ANTENATAL DIAGNOSIS OF DEVELOPMENTAL ANOMALIES

Antenatal diagnosis is possible by USG especially of hydronephrosis because of pelviureteric junction (PUJ) obstruction, anomalies of vesicoureteric junction, VUR posterior urethral valves, neurogenic bladder and nonobstructing megaureters. However, the diagnosis needs to be reconfirmed after birth by renal USG at 4–7 days and, if negative, again at the tailend of first month of life. Indications for surgery are:

- Progressively worsening renal function
- Persistent/recurrent UTI
- Hypertension.

NEUROGENIC BLADDER

This condition is characterized by urinary retention. The hypertrophied bladder, usually associated with meningomyelocele, empties partially or overflows periodically. High frequency of UTI and hydronephrosis are often found in such children. Neurogenic bladder for short periods, may be found in CNS infections like meningitis and encephalitis. Treatment is surgical bypass of the bladder by urinary diversion into an ileal bag.

OBSTRUCTIVE UROPATHY

Congenital malformations such as valves, neuromuscular bladder dysfunction, diverticulum, stricture, meatal stenosis, etc. (as also acquired conditions like calculi, blood clots, fungus balls, trauma, tumors, foreign body, tuberculosis) may produce urinary tract obstruction. Congenital ureteropelvic junction obstruction is the most frequent site in the upper urinary tract and is the most common underlying disorder leading to diagnosis of antenatally detected hydro-

nephrosis. Posterior urethral valve obstruction is the most severe obstructive uropathy. It can be diagnosed antenatally by USG. For details, See Chapter 46 (Pediatric Surgery).

Predisposing Factors

- History of hydramnios in the mother during pregnancy
- Prune belly syndrome
- VATER association (**V** for vertebral defects, **A** for imperforate anus, **T** for tracheoesophageal fistula with esophageal atresia and **R** for radial and renal dysplasia)
- Chromosomal defects, e.g. Down syndrome, XO, 13–15 and 16–18 trisomies
- Congenital heart disease
- Absent/deformed pinna
- Preauricular pits
- Hypospadias
- Sacral agenesis
- Anorectal malformations.

Manifestations

- Polydipsia, polyuria, anemia, failure to thrive (FTT), chronic irritability, recurrent UTI, weak or forceful stream, enuresis, salt wasting and hyponatremia.
- Azotemia, hypocalcemia, hyperphosphatemia and hyperchloremic metabolic acidosis are often present.
- Some degree of hydronephrosis is usual, so is hypertension.
- Vitamin D resistant rickets are likely to develop in due course of time. Distal tubular dysfunction characterized by impairment of the urinary concentration and acidification, as also disturbance of renal hydroxylation of vitamin D contribute to the development of these abnormalities.
- Obstructive uropathy is usually detected fairly late so much and so that considerable damage is already caused.

Diagnosis

- Radiological studies show renal osteodystrophy (rickets with osteoporosis)
- Intravenous pyelogram for site of obstruction
- Voiding cystourethrogram for posterior urethral valves or vesicoureteral reflux
- USG for locating the site of obstruction.

Treatment

- It is primarily surgical correction or bypass of the obstruction.
- Correction of acidosis along with supportive measures is important.

PROTEINURIA

Definition

The term, proteinuria, is employed when more than 150 mg (0.15 g) protein is found in urine in 24 hours. The share of albumin is only 30 mg/24 hours.

Measurement

Measurement of urine protein is by:

- Boiling test including treatment with sulfosalicylic acid
- Dipstick test
- 24-hour urine collection
- Urine protein/creatinine ratio which quantitates proteinuria when timed urine collection is not possible.

Types

Proteinuria may be benign or organic type.

Benign Proteinuria

- Proteinuria in this category is never more than 1g/24 hours and is never accompanied by edema. It may be postural (orthostatic), febrile, or exercise-induced.
 - In **postural (orthostatic) proteinuria**, there is 10-fold or greater increase in urine protein, in the upright position. There are no symptoms and no investigative abnormalities of the urinary tract. Though apparently a benign condition, a long-term follow-up of the child is warranted.
 - In **febrile proteinuria**, a body temperature above 38.3°C (101°F) may cause some proteinuria which resolves once fever is controlled.
 - In **exercise-induced proteinuria**, vigorous exercise may be followed by proteinuria which resolves after 48 hours of rest.

Organic Proteinuria

It may be secondary to tubular or glomerular disorders.

- **Tubular proteinuria** is characterized by migration of low molecular weight protein mainly in the alpha and beta regions so that very minimal albumin is detected in urine. It may be hereditary or acquired.
 - **Hereditary (congenital) tubular proteinuria** may accompany cystinosis, Wilson disease, Lowe syndrome, proximal renal tubular acidosis and galactosemia.
 - **Acquired tubular proteinuria** may accompany antibiotic therapy, heavy metal poisoning (mercury, gold, lead, chromium, copper and cadmium), interstitial nephritis, acute tubular necrosis and cystic diseases.
- **Glomerular proteinuria** results mostly because of increased permeability of the glomerular capillary wall. It may be **selective** when there is a loss of proteins of molecular weight up to and including albumin (as in minimal-change NS), or **nonselective** when there is loss of albumin and large molecular weight protein like IgG (as in case of most forms of glomerulonephritis). Etiological conditions leading to glomerular proteinuria include persistent asymptomatic proteinuria, NS, glomerulonephritis, tumors and drugs, etc.

HEMATURIA

Definition

The appearance of more than 5 red cells per high power field (HPF) in the sediment of a 10 mL of centrifuged fresh specimen of urine is termed **hematuria**.

Types

Hematuria may be gross macroscopic (visible to the naked eye) or microscopic (detected only by microscopic examination or dipstick of urine sediment).

- **Gross hematuria:** If originating from kidneys, it gives urine brown or cola/tea color. In case it originates from lower urinary tract (bladder and urethra), urine has a bright red or pink color and may show up clots.
- **Microscopic hematuria:** In microscopic hematuria, color of urine remains normal. This form of hematuria is detected only by microscopic examination or by dipstick of the urine sediment. It is pertinent to determine if hematuria is total, initial, or terminal.
 - **Total hematuria** is indicative of a lesion above the bladder neck.
 - **Initial hematuria** points to the source of blood along the urethra.
 - In **terminal hematuria**, areas last to be emptied of urine (trigone, bladder neck, prostate) are the source of bleeding.

A spotting of blood on the undergarments indicates that blood is coming from urethra distal to the sphincteric mechanism. Note that colored urine may result from factors other than blood. For instance, dark yellow urine may simply be the result of excessive concentration or bile pigments. Red urine may result from myoglobin, porphyrins, beets, black berries, red food coloring, phenolphthalein, urates or pyridium. Homogentisic acid may impart the urine dark brown or black color.

Etiology

Box 31.2 lists important causes of hematuria. It is noteworthy that microscopic hematuria need not essentially be a sign of renal disease. It may result from heavy exercise, viral or bacterial infections and drugs, etc.

Diagnosis

History and Clinical Examination

Diagnostic evaluation must begin with accurate history and physical examination. Make sure that the patient is not on any drug, etc. that may color the urine. Is there accompanying dysuria? Any fever, periorbital edema, backache or abdominal pain (flank, suprapubic)? Has there been any recent trauma? Any history of insertion of a foreign body into the urethra? Did the patient have a systemic infection recently? Any preceding skin or upper respiratory infection that could be a precursor of acute glomerulonephritis? Any bleeding disorder in the patient or a family member? A complete physical examination, including blood pressure determination, is important. Never miss looking for edema. The perineum and urethra need to be carefully examined.

Investigations

It is mandatory to demonstrate presence of red cells in urine microscopically. Red color of urine may well be secondary to hemoglobinuria, myoglobinuria, beeturia and metabolic products of certain drugs or poisons. A grossly bloody urine that fails to show large number of red cells points to intra-

Box 31.2 Noteworthy causes of pediatric hematuria**Renal diseases**

- APSGN
- Recurrent gross hematuria/persistent gross hematuria
 - IgA nephropathy (Berger nephropathy)
 - Idiopathic (benign familial) hematuria
 - Alport syndrome
- Membranous glomerulopathy
- SLE nephropathy
- Membranoproliferative glomerulonephritis
- Nephritis of chronic infections
- Rapidly progressive glomerulonephritis
- Good pasture disease
- Anaphylactoid purpura (Henoch-Schonlein purpura)
- Hemolytic uremic syndrome.

Infections

- Bacterial
- Infective endocarditis
- Tuberculosis.

Hematologic diseases

- Coagulopathies
- DIC
- Thrombocytopenia
- Hemophilia
- Sickle cell disease
- Renal vein thrombosis
- Stones and hypercalciuria.

Anatomical abnormalities

- Congenital malformations
- Polycystic kidneys
- Vascular abnormalities.

Drugs

- Cyclophosphamide
- Aspirin
- Kanamycin sulfate
- Aminophylline
- Troxidone
- Phenytoin
- PAS Anticoagulants
- Cephalosporin
- Bacitracin
- Methicillin
- Penicillin.

Miscellaneous

- Exercise (vigorous)
- Severe perinatal hypoxia
- Neoplasm
 - Wilms' tumor
 - Bladder papilloma
- Trauma
- Idiopathic hypercalciuria
- Factitious hematuria (Munchausen syndrome by proxy).

Abbreviations: DIC, disseminated intravascular coagulation; APSGN, acute poststreptococcal glomerulonephritis; SLE, systemic lupus erythematosus; PAS, 4-aminosalicylic acid.

vascular hemolysis resulting in hemoglobinuria or myoglobinuria. All children with established hematuria (gross) should be investigated stepwise (Box 31.3).

Treatment

Treatment depends on the causative factor(s) plus the accompanying complications.

Box 31.3 Stepwise investigations of gross hematuria

- **Step 1** relates to studies performed in all subjects:
 - CBC
 - Urine culture
 - Serum creatinine level
 - 24-hour urine collection for creatinine, protein, calcium
 - Serum C3 level
 - Ultrasound or IVP.
- **Step 2** relates to studies performed in selected subjects:
 - DNase B titer or streptozyme test if hematuria is of less than 6 months duration
 - Skin or throat cultures when appropriate
 - ANA titer
 - Urine erythrocyte morphology
 - Coagulation studies/platelet count when suggested by history
 - Sickle cell screening in all black patients
 - Voiding cystourethrography with presence of infection or when lower tract lesion is suspected
- **Step 3** relates to invasive procedures such as renal biopsy and cystoscopy. Renal biopsy is indicated for:
 - Persistent high grade microscopic hematuria
 - Microscopic hematuria plus any of the following:
 - Diminished renal function
 - Proteinuria exceeding 150 mg/day (0.15 g/day)
 - Hypertension
 - Second episode of gross hematuria
 - Cytoscopy is indicated for pink to red hematuria, dysuria, and sterile urine culture.

Abbreviations: CBC, complete blood count; IVP, intravenous pyelogram; DNA, deoxyribonucleic acid; ANA, antinuclear antibody.

URINARY TRACT INFECTION (Pyelonephritis)

Urinary tract infection is quite common in infancy and childhood, including neonatal period. Since its manifestations may often be absent or slight in pediatric patients, many a times it remains undetected until much damage has been caused to the kidneys. Incidence in the hospitalized children is as high as 8%. Some of them are admitted for some other ailment without any symptoms referable to urinary tract.

Etiological Considerations

- Urinary tract infection is decidedly more common in girls. Favorable anatomic factors render the female urinary tract more susceptible to ascending infection.
- Presence of congenital anomalies, like bladder-neck obstruction, neurogenic bladder and urethral valves, predisposes to recurrent UTI.
- Infection of skin may also act as a focus for hematogenous spread of the bacteria to the urinary tract.
- Another predisposing factor is the urethral catheterization.

Among the causative bacteria, *Escherichia coli* is the most common. *Streptococcus*, *Staphylococcus*, *Proteus*, *Klebsiella*, *Pseudomonas* and *Enterobacter* figure among other organisms that may cause UTI.

Clinical Features

- Onset may be acute or insidious.
- In symptomatic cases, manifestations include fever. It may be high and accompanied by chills, urinary

frequency, painful micturition, pain in loin, vomiting, delirium and sometimes convulsions.

- Nonspecific manifestations may be in the form of anorexia and irritability.
- A child may start wetting his bed after having had dry nights.
- Excessive vomiting and diarrhea may cause dehydration.
- Occasionally, it may present as meningitis-like manifestations.
- Jaundice may occur, especially in infants.

To sum up, UTI of childhood is a great mimicker. It may simulate acute abdomen, meningitis or diarrhea.

Diagnosis

The characteristic finding is pyuria. Since it may be absent at one or the other stage, repeated examinations of urine should be done carefully. Slight proteinuria and hematuria may occur. Urine culture is the gold standard for diagnosis of UTI. The best is to culture, within an hour, the freshly voided midstream specimen of urine. In infants and neonates, you may need to obtain urine by suprapubic bladder aspiration or urethral catheterization.

Anemia is present in a long-standing UTI. Total leucocyte count (TLC) and erythrocyte sedimentation rate (ESR) are high. Imaging studies (ultrasound, dimercaptosuccinic acid {DMSA} renal scan, MCU) are strongly indicated in case of UTI under the age of 2 years and recurrent UTI in older children.

Treatment

The major aim of management is preventing renal scarring and its complications in symptomatic UTI.

Specific Treatment

Asymptomatic bacteriuria needs no treatment. As soon as the diagnosis of UTI is made on the basis of quantitative pyuria, specific chemotherapy, to eradicate the infection, should be initiated. The drug that the physician considers most appropriate should be started. Later, if necessary, it may be changed depending on the culture and sensitivity report as also on patient's response.

- **First 3 months of life and complicated UTI:** Therapy of choice is third generation cephalosporin (cefotaxime) or an aminoglycoside. Later, oral medication suffices. Total duration of therapy should be 10–14 days. Children (<3 months age) and those with complicated UTI (high fever, i.e. >39°C, persistent vomiting, dehydration, renal angle tenderness) need to be hospitalized.
- **After 3 month's age and uncomplicated UTI:** Oral therapy with cefixime, co-amoxiclav, ciprofloxacin, ofloxacin or cephalixin for 7–10 days is good enough. A single bolus dose of chemotherapy in childhood UTI, using agents such as fosfomycin trometamol (monuril), is effective.

Recurrence

For a recurrence, medication may be given for an extended duration of 2–4 weeks. If the response is poor or frequent

recurrences of the infection occur, USG is indicated. **617** More sophisticated imaging studies include voiding cystourethrography (VCUG) under 2 years age and DMSA scan under 5 years age. If correctable surgical lesions are present, these require repair. For frequently-recurring UTI, a prolonged prophylactic therapy for a year or even more may be given in doses that are only half of the recommended for an active infection. Moreover, the total dose may be given only once a day at bedtime.

Supportive Measures

- Control of high pyrexia by tepid sponging and/or an antipyretic agent.
- A liberal fluid intake.
- Alkalinization of urine to provide relief from dysuria.

ACUTE GLOMERULONEPHRITIS

Acute glomerulonephritis (AGN) manifesting by sudden onset of hematuria, oliguria, edema and hypertension, is a common pediatric problem. About 90% renal diseases of childhood is accounted by it. On an average, it is responsible for about 2–4% of pediatric admissions in India. Incidence in the western countries is far less.

Etiology

Though most cases are of acute poststreptococcal glomerulonephritis (APSGN), a large number of conditions are incriminated in its etiology (Box 31.4).

Diagnosis

Diagnosis is confirmed by complete urinalysis, kidney function tests (blood urea, creatinine), serum complement (C3), ASO titer. If suspected active galactic nuclei (AGN)

Box 31.4 Causes of acute glomerulonephritis

Postinfectious

- **Bacterial:** Group A beta-hemolytic streptococci, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Salmonella*, *Leptospira*, *Treponema pallidum*
- **Viral:** Hepatitis B, hepatitis C, CMV, EBV, Varicella, Coxsackievirus, Echovirus, paravirus
- **Protozoa:** *Plasmodium malariae*, *Plasmodium falciparum*, *Toxoplasma gondii*, *filaria*
- **Miscellaneous:** Infective endocarditis, sepsis of shunts, prostheses, etc

Vasculitis

- HSP
- Microscopic polyarteritis
- Wegener's granulomatosis

Collagen disorders

SLE

Miscellaneous

- IgA nephropathy
- Membranoproliferative glomerulonephritis
- Hereditary nephropathy.

Abbreviations: SLE, systemic lupus erythematosus; IgA, immunoglobulin, CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSP, Henoch-Schönlein purpura.

618 type is other than APSGN, kidney biopsy is needed. Thus indications of kidney biopsy are:

■ **At presentation**

- Unusual presenting features such as fever, rash, arthritis and heart disease
- Mixed features of AGN and nephritic syndrome
- Normal ASO titer and C3
- High blood urea
- Anuria warranting dialysis.

■ **During course of treatment**

- Heavy hematuria persisting beyond 3–4 weeks
- Nephrotic range proteinuria (3 or 4 plus) beyond 2 weeks
- Low complement C3 beyond 12 weeks
- Proteinuria persisting beyond 6 months.

Treatment

Broadly, it revolves around control of hypertension, oliguria and edema together with restriction of fluids, sodium and potassium.

ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Definition

Acute poststreptococcal glomerulonephritis (APSGN) is characterized by sudden onset of hematuria, oliguria, edema and hypertension following an infection with Group A beta-hemolytic streptococcus (GAS). It occurs most often beyond the age of 2–3 years. Most subject are school-age children. Males suffer more frequently.

Etiopathogenesis

In all probabilities, it results secondary to a preceding streptococcal (*beta-hemolyticus type 12*) infection of throat or skin. A history of upper respiratory infection, infected scabies or impetigo, 7–14 days previously is positive in most of the patients.* In some, it may complicate scarlet fever. It is believed to be an immune-mediated disease. Pathologically, the kidney suffers as a result of **trapping in** of the soluble antigen-antibody complexes. Kidney biopsy shows proliferation and swelling of the endothelial cells. This leads to diminished blood flow through the kidney.

Clinical Features

- A typical case suffers from sore throat or streptococcal infection elsewhere.
- This is followed 1–2 weeks later by acute onset of fever, puffiness of the face, especially around the eyes (Fig. 31.3) and smoky or frankly bloody urine.
- The child may have vomiting, headache, malaise and oliguria.
- Variable degree of hypertension is usual. Occasionally, the child may be brought to the hospital in a state of hypertensive encephalopathy.
- Acute renal shutdown and CCF are the other serious complications.

* Unlike the experience in the Europe, the antecedent streptococcal infection in Indian patients is most often that of skin rather than respiratory tract.



Fig. 31.3: Acute glomerulonephritis. Note the periorbital puffiness in a 2-year-old. He presented with gross edema of face, hematuria and hypertension (BP 110/70 mmHg).

- Manifestations in some cases may be too mild to persuade the parents to bring the child to the hospital. Nephritis in such cases may never be detected. In others, several urine examinations may be needed to be sure of the diagnosis.

Diagnosis

Any child, who suddenly starts passing smoky, dirty-brown urine, especially if associated with puffiness of the face, should be investigated for acute nephritis. Urinalysis shows mild to moderate albuminuria, few to several red cells, few pus cells and many granular casts. The output is reduced. ASO titer and ESR are usually high.

Blood urea touches the upper limit of normal or may be slightly increased; same is true for potassium. Since most of the cases have already been given antibiotics before they land up in the hospital, throat swab may only occasionally show streptococci.

Differential Diagnosis

It is from HUS, acute glomerulonephritis occurring in vasculitis (anaphylactoid purpura, SLE, polyarteritis nodosa, Wegener's granulomatosis), membranoproliferative glomerulonephritis, hepatitis B, infective endocarditis, acute pyelonephritis, NS accompanied by hematuria, IgA nephropathy and familial nephropathy (Alport syndrome). These conditions are easily excluded by their associated features.

Complications

A child suffering from acute nephritis is at a potential risk of one or more of the following serious complications:

- Hypertensive encephalopathy
- CCF
- Acute kidney injury (AKI).

Treatment

- **Supportive measures:** During acute phase, bed rest (flexible) and restriction of proteins, sodium, potassium and fluids are desirable. This is more so when oliguria is present. As soon as the clinical state returns to normal, child should be permitted normal activity as well as intake.
- **Antibiotics:** Antibiotic cover, preferably with penicillin, should be given for about a week in the presence of the coexisting pharyngitis or pyoderma only.

Treatment of Complications

Apart from the aforesaid measures, the treating physician should keep an eye on the possibility of complications such as:

- **Hypertension:** Significantly high blood pressure should be treated with nifedipine, atenolol, reserpine, propranolol or alpha-methyldopa.
- **Congestive cardiac failure:** It may need adequate digitalization and/or IV furosemide, a venesection with removal of 100–200 mL blood or application of rotating tourniquets to decrease venous return to heart. Dopamine infusion is also of value.
- **Prolonged oliguria/anuria:** This requires dialysis. Other indications of dialysis are AKI, fluid overload and severe dyselectrolytemia.
- **Seizures:** It is better to avoid phenobarbital* and use some other anticonvulsant like diazepam or lorazepam.
- **Renal failure:** The best treatment is peritoneal dialysis. Initially, hypertonic solutions to get rid of the excess fluid and the isotonic solutions to bring down the high blood urea and potassium levels are of value. Other measures for hyperkalemia include administration of cation-exchange resins and 10% glucose with small doses of insulin.

Prognosis

As a rule, prognosis in APSGN is excellent. Around 95% patients completely recover though hematuria may persist for many months or 1–2 years. Hypertension usually takes 2–3 weeks to settle. Recurrences are infrequent. About 1–5% may die and another around 1–5% pass on to chronic glomerulonephritis.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (Crescentic Glomerulonephritis)

Definition

It is a rapidly progressive glomerular injury characterized by presence of crescents in more than half of the glomeruli.

Types

Three major forms are recognized:

1. **Immune complex crescents glomerulonephritis:** It is characterized by immunoglobulin deposits, C3 deposits, either low C3 or high C3.

2. **Pauci-immune crescents glomerulonephritis:** It is characterized by vasculitis involving small vessels, positive antineutrophil cytoplasmic antibodies and scanty immune deposits.
3. **Antiglomerular basement membrane glomerulonephritis:** It is characterized by linear IgG deposits and anti-glomerular basement membranes (GBM) antibodies. Greater the proportion of glomerular involvement, more is the severity of the disease.

Diagnosis

Renal biopsy is the only means available to establish the diagnosis. Any child with severe AGN in whom the resolution fails to occur within 1–2 weeks is a candidate for renal biopsy.

Treatment

It comprises of IV and oral steroids and IV cyclophosphamide followed by maintenance dose of immunosuppressants. In pauci-immune crescents glomerulonephritis and Goodpasture syndrome, plasmapheresis should be the choice.

OTHER CONDITIONS WITH GLOMERULONEPHRITIS

HENOCH-SCHONLEIN PURPURA (HSP) (Anaphylactoid Purpura)

In Henoch-Schonlein purpura, most common vasculitis of childhood, renal involvement is in the form of mesangial proliferation with mesangial deposition. Serum IgA levels are high. They have only microscopic hematuria with proteinuria. Though most subjects have a mild disease which resolves on its own, rarely manifestations of NS, including crescentic type, may be there. Therapy is with steroids and cyclophosphamide. Maintenance is with steroids plus azathioprine. Prognosis depends on type of renal involvement.

IMMUNOGLOBULIN A NEPHROPATHY

IgA deposition in mesangium and capillary wall of glomeruli may initially cause mild proteinuria and microscopic hematuria which take shape of gross recurrent hematuria following upper respiratory infections. Later, NS may develop. Angiotensin-converting-enzyme (ACE) inhibitors are the drugs of choice. Once NS has developed, therapy is with steroids plus alkylating agents.

SLE-RELATED NEPHRITIS

Systemic lupus erythematosus (SLE) may cause acute nephritis and NS. Even asymptomatic proteinuria and hematuria may occur. Lupus nephritis, though rare, is rapidly progressive, causing:

- Deposition of IgG and C3, CLq and IgA.

* Phenobarbital may accumulate to dangerous level in patients with poor renal function. It is almost entirely excreted by the kidneys.

- 620 ■** Diffuse proliferative glomerulonephritis in which C3 levels are decreased and antinuclear and double-stranded deoxyribonucleic (dsDNA) autoantibodies present.

Mortality is from end-stage renal disease and super-added infections. Therapy is in the form of steroids and cytotoxic agents like cyclophosphamide.

RENAL TUBULAR DISORDERS

Renal Tubular Acidosis (RTA)

This state is characterized by hyperchloremic metabolic acidosis resulting from defective urinary acidification. Four major varieties are recognized, viz:

1. Type I (distal RTA)
2. Type II (proximal RTA)
3. Type III (combined proximal and distal)
4. Type IV (mineralocorticoid deficiency).

Type I (Distal RTA)

It occurs as a deficiency of secretion of hydrogen ion (urinary ammonium and titrable acid) by distal tubule and collecting duct, increased back diffusion of hydrogen ions, or, perhaps, some other mechanism. Severe hyperchloremia and moderate hypokalemia result from loss of sodium bicarbonate. Despite severe systemic acidosis, pH of urine cannot be reduced below 5.8. Manifestations include FTT, muscular weakness, paralysis, dehydration, pyrexia, polyuria, polydipsia, refractory rickets and nephrocalcinosis.

It may occur as an isolated condition, or secondary to interstitial nephritis (as in pyelonephritis, obstructive uropathy, SLE, sickle-cell nephropathy, cirrhosis, Ehler-Danlos syndrome, nephrocalcinosis, transplant rejection, etc.) and toxins (amphotericin B, lithium, toluene, etc). Alkali, 3 mEq/kg/day, under careful monitoring corrects the acidosis.

Type II (Proximal RTA)

It results from reduced reabsorption of bicarbonate by proximal tubules which are ascribed to deficient carbonic anhydrase production. The distal tubules having a capacity to reabsorb a maximum of 15% of the filtered load fail to cope with 40% of the filtered load. Around 25% of it is, therefore, lost in urine. Hyperchloremia and potassium loss because of aldosterone secretion finally results. Manifestations include FTT, refractory rickets and, infrequently, nephrocalcinosis. It may occur as an isolated condition or secondary to Fanconi syndrome. This syndrome is characterized by glycosuria, phosphaturia, aminoaciduria, carnitinuria and proximal RTA.

Fanconi syndrome, besides the primary form, may occur secondary to:

- **Inherited disorders:** Cystinosis, Lowe syndrome (Box 31.5), galactosemia, hereditary fructose intolerance, Wilson disease, tyrosinemia, medullary cystic disease.
- **Acquired disorders:** Heavy metals, expired tetracycline's, 6-mercaptopurine, NS, interstitial nephritis and hyperparathyroidism.

Alkali, 10–15 mEq/kg/day (note the dose is much higher than that in distal RTA), along with potassium is needed to correct the acidosis.

Box 31.5

Two important causes of secondary Fanconi syndrome

Cystinosis

- **Definition:** An autosomal recessive disorder, cystinosis is characterized by a very high level of free lysosomal membrane protein which gets deposited as crystals in the cornea, conjunctiva, bone marrow, leucocytes and lymph nodes.
- **Etiology:** The cause is a defect in cystinosis—lysosomal membrane protein which is responsible for transporting cystine from lysosomes into the cytosol.
- **Clinical features:** Infantile nephropathic form is the most common. When it occurs in later years, manifestation includes photophobia, hepatosplenomegaly and blond hair.
- **Diagnosis:** In a clinically suspected case, the following tests need to be done:
 - Slit lamp microscopy for cysteine crystals in cornea.
 - Elevated levels of cysteine in polys or cultured fibroblasts.
- **Prenatal diagnosis** is available. It involves measurement of cysteine levels in chorionic villi of cultured amniotic fluid cells.
- **Complications:** Hypothyroidism, diabetes mellitus and end-stage renal failure.
- **Treatment:** Attention to metabolic acidosis, dyselectrolytemia, oral and topical; cysteamine.

Lowe syndrome

(Oculocerebrorenal Syndrome of Lowe)

An X-linked disorder, this condition is characterized by Fanconi syndrome, ocular defects (buphthalmos, corneal degeneration, strabismus and congenital cataracts), severe rickets, seizures, neurodevelopmental delay and hypotonia. Remarkable calciuria may be present. Diagnosis is established by:

- Mutational analysis of affected gene (OCRL).
- Measurement of activity of the enzyme, phosphatidylinositol biphosphate 5-phosphatase in cultured fibroblasts.
- Most children succumb to progressive chronic renal insufficiency early in infancy.

Type III (Combined proximal and distal RTA)

It is associated with deafness, blindness and osteoporosis.

Type IV (Hyperkalemic)

It is the result of inadequate production or lowered distal tubular responsiveness to aldosterone. Hyperkalemic hyperchloremia acidosis that tends to reduce the urine pH to under 5.5 is the net outcome. This variety of RTA may be secondary to adrenal disorders (Addison disease, congenital adrenal hyperplasia, primary hypoaldosteronism), hyporeninemic hypoaldosteronism (obstruction, pyelonephritis, interstitial nephritis, diabetes mellitus, nephrosclerosis), or pseudohypoaldosteronism. Obstructive uropathy is, undoubtedly, its most common cause.

NEPHROGENIC DIABETES INSIPIDUS (NDI)

Definition

This condition is characterized by failure of the kidneys to respond to antidiuretic hormone (ADH) though the levels of this hormone are quite high.

Types

Two varieties are recognized.

1. In **primary NDI**, a rare disorder with usually X-linked recessive inheritance, the distal tubule is not able to

respond to ADH. A dramatic history of polyuria and polydipsia in infancy with hypernatremic dehydration in infancy is classical in males with primary NDI. In females with primary NDI, manifestations are mild and may be detected later in life.

2. In **secondary NDI**, there may be diminution of hypertonic medullary gradient because of solute diuresis or failure of tubules to reabsorb sodium chloride and urea. It can also result from induced tubular unresponsiveness.

Treatment

It revolves around:

- Adequate fluid and calorie intake
- Reduction of sodium intake to reduce urinary solute load
- Diuretic therapy (chlorthiazide 20–40 mg/kg/day in divided doses)

Subjects with primary NDI not responding to this therapy should be administered indomethacin which acts by inhibiting prostaglandin synthesis.

BARTTER SYNDROME

Definition

This rare form of renal potassium wasting, presumably a primary defect in the ascending limb of the loop of Henle, is characterized by severe hypokalemia, excessive potassium excretion, normal blood pressure, vascular insensitivity to pressor agents, elevated plasma renin and aldosterone and metabolic alkalosis.

Clinical Features

- Failure to thrive, muscle weakness, polyuria, polydipsia, dehydration and constipation.
- Muscle cramps and carpopedal spasms as additional features in older children.

Treatment

Therapy resolves around:

- Providing adequate nutrition and maintaining serum potassium level above 3.5 mEq/L.
- Drug triamterene, 5–10 mg/kg/day, or indomethacin, 3–5 mg/kg/day, in case of failure of potassium therapy in as high a dose as 250 mEq/day.

GITELMAN SYNDROME (Bartter Syndrome Variant)

Gitelman syndrome is an autosomal recessive condition characterized by a defect in the apical thiazide sensitive sodium chloride cotransporter (NCCT) in distal tubules. Clinical features are much milder than Bartter syndrome.

ACUTE KIDNEY INJURY (Acute Renal Failure)

Definition

Acute kidney injury, previously called **acute renal failure (ARF)**, refers to severe renal dysfunction, characterized by

a sudden reduction of urine excretion to under 10 ml/kg body weight, indicating marked oliguria or even anuria. As a consequence, retention of nitrogenous wastes as well as other metabolic derangements results.

Manifestations resulting from overhydration, anemia, uremia, acidosis and hyperkalemia are generally present. The **oliguric phase** is followed within 7–10 days by **diuretic phase** in which urine flow rises and child's general condition improves. During the **recovery phase**, urinary excretion falls and renal function gradually returns to normal. Some cases may not show satisfactory improvement. They often pass on to chronic renal failure.

Etiology

Box 31.6 gives the list of important conditions that may lead to AKI.

Evaluation

Clinical

A history of severe gastroenteritis, severe vomiting, severe diarrhea is usual in prerenal AKI. It is important to enquire about the history of oliguria though there may be AKI even without it (nonoliguric AKI in intravascular hemolysis and nephrotoxicity).

Investigative

The investigations that are essential in the proper management of ARF, are highlighted in Box 31.7 and 31.8.

Box 31.6 Etiology of acute kidney injury

Prerenal

- Dehydration
- DKA
- Hypovolemia in nephritic syndrome, burns, bleeding, shock, trauma, CCF
- Too little sodium in IV fluids.

Renal

- Acute glomerulonephritis
- Hemolytic uremic syndrome
- Renal vein thrombosis
- Acute tubular necrosis from toxins
- Neoplasm
- Downing
- Iatrogenic.

Postrenal

- Bladder neck obstruction
- Urinary tract obstruction from other congenital lesions or pus collection
- Sulfonamide crystals.

Abbreviations: DKA, diabetes ketoacidosis; CCF, congestive cardiac failure; IV, intravenous.

Box 31.7 Important investigations in ARF

- **Blood:** Complete blood picture (CBP), urea, creatinine, electrolytes (sodium, potassium, calcium, phosphate, bicarbonate, pH)
- **Urine:** Urinalysis, culture
- **Sodium:** Osmolality, fractional excretion
- **Chest X-rays:** Pulmonary edema, cardiomegaly
- Abdominal ultrasonography.

Abbreviation: ARF, acute renal failure.

Box 31.8 Specific investigation for a suspected etiology of AKI

Suspected etiology	Investigation
Hemolytic-uremic syndrome	CBP, peripheral smear, platelet count, reticulocyte count, C3, LDH; stools for shigatoxin
Rapidly progressive glomerulonephritis/acute glomerulonephritis	ASO titer, C3, antinuclear antibodies, antineutrophil cytoplasmic antibody
Thrombosis (arterial or venous)	Doppler ultrasonography
Conditions in which a specific pathological diagnosis is on the card	Kidney biopsy

Abbreviations: CBP, complete blood picture; LDH, lactate dehydrogenase; ASO, antistreptolysin O; AKI, acute kidney injury.

Management

General Measures

- Acute kidney injury child needs intensive care with maintenance of record of daily weight, intake-output and blood pressure (BP).
- While patient's acute problems are being tackled, efforts should also be directed at finding the etiologic factor responsible for the shutdown.
- Though prophylactic antibiotics are not required,
 - Appropriate preventive measure is warranted, e.g. aseptic techniques, vigilance over IV lines, injection sites and avoidance of long-term catheterization.
 - Treatment of a superimposed infection is necessary.
- Nephrotoxic drugs (aminoglycosides, nonsteroidal anti-inflammatory drugs [NSAIDs], ACE inhibitors, amphotericin B) should be avoided.

Maintenance of Fluid and Electrolyte Balance

The sheet-anchor of management is the control of fluid and electrolyte balance. An accurate strict intake and output chart is required to be maintained.

- **Fluid repletion:** This is mandatory in perennial AKI as a result of dehydration. To correct dehydration, 20–30 mL of normal saline or Ringer lactate is administered IV over nearly an hour. Response to fluid repletion is in the form of increased urine output. If diuresis fails to occur, furosemide, 2–3 mg/kg is administered. If no response, diagnosis of AKI stands established.
- **Fluid restriction:** In a child with established AKI, continuing fluids may lead to fluid retention, edema, hypertension and heart failure. Now, daily intake of fluids should be restricted to losses through perspiration, vomiting, stools and breathing. This may preferably be given by mouth. If IV isotonic saline or Ringer lactate is to be given, 20–30 ml/kg of body weight in one hour is the recommendation.

If the underlying cause of anuria is excessive blood loss or burns, a blood transfusion (10–20 ml/kg) is indicated.

Attention to Complication

- **Hyperkalemia:** In case of hyperkalemia, any further administration of potassium should be avoided. To

reduce the potassium level, the following measures may be helpful:

- IV calcium gluconate (10%), 0.5–1 ml/kg, over 5–10 minutes
- Salbutamol nebulization, 5–10 mg
- Sodium bicarbonate (7.5%), 1–2 ml/kg over 10–15 minutes
- IV dextrose (10%), 0.5–1 g/kg plus insulin, 0.1–0.2 units/kg
- For rapid control of fulminant hyperkalemia, administration of glucose-calcium, gluconate-insulin infusion is indicated. Alternatively, hypertonic sodium lactate or bicarbonate solution, 3 mEq/kg, is a useful measure for transitory relief
- Administration of a cation-exchange resin in the sodium form. Resonium A in a dose of 1 mg/kg/day (in 2 divided doses) lower serum potassium by 1 mEq/L.
- Dialysis is needed in case of persistent hyperkalemia not responding to the above treatment
- **Hyponatremia:** Hyponatremia with plasma sodium is less than 125 mEq/L is likely to cause seizures and even encephalopathy. If plasma sodium is 120–125 mEq/L, fluid restriction usually resolves the problem. If the level is less than 120 mEq/L or the patient is symptomatic, 3% saline, 6 ml/kg may be administered to raise serum sodium level by 5 mEq/L cautiously. Risk of hypertension and fluid overload exists with this therapy.
- **Hypocalcemia:** In case of hypocalcemia, 4–8 g/kg by mouth or smaller amounts IV of calcium gluconate should be administered. In order that this therapy proves effective, aluminium hydroxide gel, 1–2 teaspoonful 3–4 times daily, should be given. Also, care should be exercised to restrict phosphate-rich foods like milk. It is difficult to bring up serum calcium in the presence of hyperphosphatemia.
- **Hyperphosphatemia:** Besides phosphate binders such as calcium carbonate and aluminium hydroxide and milk products known for high phosphate content should be avoided. Diet needs to be rich in protein.
- **Severe anemia:** Blood transfusion.
- **Pulmonary edema:** IV furosemide, 2–4 mg/kg, oxygen
- **Hypertension:** Severe hypertension needs to be controlled employing furosemide, nitroprusside, labetalol, etc.
- **Heart failure:** It is usually secondary to severe hypertension. Hence, control of severe hypertension is very important; sometime endotracheal intubation and/or assisted ventilation.
- **Metabolic acidosis:** If remarkable acidosis coexists, it should be corrected with sodium lactate or bicarbonate.

Dialysis

Dialysis aims at removal of endogenous and exogenous waste products/toxins and maintains fluid, electrolyte and acid-base balance in anticipation of restoration of renal function. Indications of dialysis are:

- Persistent hyperkalemia (serum potassium >6.5 mEq/L) despite appropriate treatment

Box 31.9 Types of dialysis

- **Peritoneal Dialysis:** This is a simple and the initial dialysis modality. Dialysis fluid (dialysate), 3–40 ml/kg is infused and allowed to remain in peritoneal cavity for around 45 minutes. Thereafter, it is drained employing siphon concept. In the beginning around 25 cycles are conducted. Risk: Peritonitis.
- **Hemodialysis:** It is expensive and cumbersome, needing hemodialysis machine, specialized expertise and nursing in an institution.
- **Continuous renal replacement therapy (CRRT):** CRRT is quite expensive, involves continuous hemofiltration through extracorporeal blood purification and is of quite a few types. It is indicated in difficult cases not responsive to hemodialysis.
- **Slow long extended daily dialysis:** This provides added benefits of hemodialysis and CRRT.

- Progressive metabolic acidosis
- Rise in blood urea at a rate exceeding 100 mg/dL per 24 hours
- Pulmonary edema from fluid overload
- Severe hypertension from fluid overload
- CCF
- Severe metabolic acidosis
- Hypo or hypernatremia
- Uremic encephalopathy
- Further aggravation in clinical condition of the child.

Remember that dialysis must be initiated slowly. Or else, the patient may develop symptoms ranging from nausea and vomiting to severe headache and convulsions. The probable explanation is rapid removal of urea from blood is far too much for the slow removal exercised by the brain and results in cerebral edema. This complication is called **dysequilibrium syndrome**. It is more often encountered with hemodialysis. Type of dialysis employed are given in Box 31.9.

Nutrition

Diet should be primarily in the form of carbohydrates and fat, providing at least 60–80 kcal/kg. Proteins should be restricted to 1–1.2 g/kg in infants and 0.8 g–1.2/kg in children to cut down endogenous catabolism. The latter predisposes to hyperkalemia and azotemia. It is important to provide supplements of vitamins and micronutrients.

Prognosis

Overall mortality is around 30%. Poor prognostic signs include:

- Associated sepsis
- Associated HUS
- Delayed referral and initiation of appropriate treatment
- Cardiac, hepatic or respiratory failure.

CHRONIC KIDNEY DISEASE

(Chronic Renal Disease, Chronic Kidney Failure, Chronic Renal Failure)

Definition

Chronic kidney disease, currently the preferred **semantic**, is defined as a permanent kidney injury characterized by

structural and/or functional abnormalities with or without **623** fall in GFR, spread over a minimal period of 3 months.

Staging

Staging of CKD in children (>2 years), based on GFR, is as follows:

- **Stage 1:** GFR 90–100 ml/minute/1.73 m². Only slight kidney damage with normal or increased GFR.
- **Stage 2:** GFR 60–90 ml/minute/1.73 m². Kidney damage with slightly reduced GFR.
- **Stage 3:** GFR 30–60 ml/minute/1.73 m². Kidney damage with moderately reduced GFR.
- **Stage 4:** GFR 15–30 ml/minute/1.73 m². Kidney damage with severely reduced GFR.
- **Stage 5:** GFR <15 ml/minute/1.73 m². Kidney failure or on dialysis.

Etiology

Box 31.10 lists important causes of CKD. However, it must be emphasized that whereas anatomic abnormalities like hypoplasia, dysplasia, obstruction and malformations top the list before 5 years of age, acquired glomerular disease (glomerulonephritis, HUS), or hereditary disorders (Alport syndrome, cystic disease) dominate the scene in later years.

Box 31.10 Etiology of chronic kidney disease**Glomerulonephritis**

- Primary
- Secondary
 - Systemic lupus erythematosus
 - Henoch-Schönlein purpura
 - IgA nephropathy

Reflux nephropathy

- Primary
- Secondary

Renal infections

- Hemolytic uremic syndrome
- Pyelonephritis with or without reflux nephropathy
- Tuberculosis

Obstructive nephropathy/uropathy

- Posterior urethral valves
- Bilateral calculi
- Bilateral pelviureteric junction obstruction (stenosis)

Congenital/developmental anomalies

- Polycystic kidneys
- Bilateral renal hypoplasia

Storage Diseases

Amyloidosis

Tumors

Bilateral Wilms' tumor

Hereditary/familial Nephropathies

- Alport syndrome
- Nephronophthisis
- Polycystic kidneys

Miscellaneous

- Renal cortical necrosis
- Renal vein thrombosis.

624 Clinical Features

- Manifestations include increased thirst, frequent passage of urine, progressive anemia, hypertension, growth retardation, rickets and bone pains.
- In late stage, acidotic breathing, anorexia, nausea, vomiting, muscular weakness, peripheral neuropathy, itching, purpura, cardiomyopathy and pericarditis are present.
- Blood pressure may be elevated with hypertensive changes in the fundus.
- In some children, FTT, anemia, hypertension and bony deformities may well be the first manifestation of CKD without any prior history of renal disease.
- Superadded infection, as a result of defective granulocytic function and impaired cellular immune function, is frequent, and often contributes to terminal renal failure and mortality.

Diagnosis

Over and above good history and clinical work-up, the following investigations are needed:

- Complete blood picture (CBP)
- Blood urea, creatinine, electrolytes, pH, bicarbonate, calcium, phosphorous and alkaline phosphate
- Blood transferring and transferring saturation (especially in anemic patients)
- GFR
- Imaging.

Treatment

Diet

Diet in CKD needs particular attention.

- **Protein:** The protein intake needs to be at least 1.5 g/kg/day (100 percent of recommended dietary allowances {RDA}). It should be of highest biological value, e.g. egg white, milk, meat, fish and fowl. Limiting protein intake to a very low level not only fails to stop progression of renal failure, but also causes growth failure.
- **Energy:** The calorie intake should be 80–100 percent (or more in the event of existing growth deficit) of RDA.
- **Phosphate:** Low phosphate milk should be preferred.
- **Potassium:** High potassium foods and excessive intake of sodium should be avoided.
- **Sodium:** Polyuric children need sodium supplements. On the other hand, sodium intake needs restriction in children with chronic glomerulonephritis.
- **Vitamins:** Supplementary vitamins (water soluble), calcium and zinc may be administered.
- **Water:** Water intake should be liberal, ensuring that dehydration is prevented at all costs. Else, the subject runs the risk of going into enhanced azotemia. However, in chronic glomerulonephritis water intake needs to be restricted.

Attention to Complications/Comorbidities Acidosis

Acidosis with serum bicarbonate falling below 20 mEq/L occurs when GFR falls below 50 percent of normal needs to

be treated with sodium bicarbonate tablets (2–3 mEq/kg/day, may be increased as required) to raise the serum bicarbonate level above 18–20 mEq/L.

Anemia

Anemia with hemoglobin falling below 6 g/dL needs a packed red cell transfusion (10 ml/kg) cautiously. The new modality, recombinant human erythropoietin or synthetic erythropoietin has eliminated the need for repeated transfusions, thereby preventing complications such as iron overload, cytotoxic antibodies and superimposed infections.

Maintaining a good hemoglobin level improves fitness of the subject. Erythropoietin is, however, very expensive and not yet freely available in developing countries. Its indication is a hematocrit under 0.27 or transfusion dependence. The dose is 50 units/kg/week subcutaneously (SC) in single or two divided doses. If response is inadequate, dose is increased by 25 units/kg/week. Once target (hemoglobin 11 g/dL) is reached, dose is reduced by 12.5–25 units/kg/week.

Most common side effect of erythropoietin is hypertension followed by painful injection site, hyperphosphatemia, vascular access thrombosis and influenza-like symptoms. Most frequent cause of unresponsiveness of the subject to it is iron-deficiency anemia followed by infection, aluminium toxicity, severe hypoparathyroidism, hemolysis and bone marrow dysplasia.

Hypertension

Hypertension needs to be appropriately treated to maintain diastolic values under 80 mm Hg. Acute hypertensive emergency is best handled with sublingual nifedipine or IV diazoxide, at times with furosemide. Therapy of sustained hypertension revolves around furosemide, propranolol and hydralazine. Minoxidil and captopril should be reserved for resistant cases only.

Mineral Bone Disease (Renal Osteodystrophy)

Renal osteodystrophy needs to be managed with low phosphate diet supported by an antacid, calcium carbonate. The latter not only binds phosphate in the GIT, but also enhances its fecal excretion. Aluminium antacid must be avoided to safeguard against risk of aluminium poisoning. Supplementation with calcium corrects hypocalcemia which is usual in chronic renal failure (CRF).

Large amounts of vitamin D₃ (25,000–100,000 IU/day) or calcitriol (1,25-dihydroxycholecalciferol) 15 ng/kg/day in two divided doses or 0.5–1.0 µg thrice a day, which is many times more potent than vitamin D₃ are initially indicated in:

- Persistent hypocalcemia despite appropriate corrective measures.
- Osteodystrophy as confirmed by high serum alkaline phosphatase level and radiologic evidence of rickets. Following occurrence of healing of rickets, dose of vitamin D₃ is reduced.
- Serum parathyroid hormone (PTH) over 2–3 times the normal.

Infections

Infections, especially UTI, must be energetically treated with appropriate antibiotics else, further deterioration in the patient's condition is bound to occur.

Miscellaneous

- **Symptomatic therapy** with antihistaminics is justified in the presence of itching, anorexia and vomiting in advanced CRF.
- **Drug dosage** needs careful monitoring since, when given in normal recommended doses, these may cause toxicity in CRF. Potentially nephrotoxic drugs must be avoided.
- **Immunization** should be on normal lines to safeguard against infections which can have further deleterious effect on the renal status. All live vaccines must be given before transplantation. Until 6 months after transplantation, vaccines are not given.

Renal Transplantation

Renal transplant becomes the final remedial therapy in end-stage renal disease/failure.

HEMOLYTIC-UREMIC SYNDROME

Hemolytic-uremic syndrome (HUS), a systemic disease is the most common cause of acute renal failure in young children. Its incidence is on an increase.

Definition

HUS is characterized by a triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure.

Etiology

The exact etiology is not yet known. Most cases in India show association with acute shigellosis. Other bacterial pathogens incriminated in its etiology include *Salmonella*, *E. coli* (O157:H7), *Clostridia*, *Campylobacter*, *Yersinia* and *Streptococcus pneumoniae*. Viruses such as coxsackie, echo, influenza, varicella, Epstein-Barr, infectious mononucleosis, measles, mumps and polio are also blamed for its development. Remaining associations of HUS include oral contraceptive, mitomycin or cyclosporine A use, endotoxemia, SLE, malignant hypertension, preeclampsia, postpartum renal failure, radiation nephritis, and complement deficiency.

Role of genetic factors in etiology of HUS is unclear though the syndrome is known to occur in more than one member of a family. It has been postulated that there may be absence of a plasma factor that stimulates endothelial cell prostacyclin production.

Pathogenesis

The endothelial cell injury constitutes the hallmark of HUS. The brunt of this injury falls chiefly on the kidneys. Vascular endothelial injury in the kidney causes localized clotting. The hemolytic anemia results from damage to the RBCs as they pass through the altered vasculature.

Thrombocytopenia is the result of adhesion or destruction of platelets in renal microvasculature. There is, as a rule, no evidence of disseminated intravascular coagulation (DIC).

Pathology

The early alterations in glomeruli include thickening of capillary wall, narrowing of capillary lamina and widening of mesangium. Deposition of a granular amorphous material appears to be responsible for these changes. Cortical necrosis may also be observed as a result of fibrin thrombi. In advanced cases, partial or total sclerosis of glomeruli and vascular occlusion are noteworthy features.

Clinical Features

Hemolytic-uremic syndrome occurs mostly in infants and children under 4 years of age.

- Onset is acute.
- 5–10 days following an episode of gastroenteritis with often bloody diarrhea, or an upper respiratory infection, manifestations such as pallor, irritability, weakness, lethargy and oliguria make their appearance.
- In addition, dehydration, edema, petechiae, hypertension and hepatosplenomegaly may be found on clinical examination.
- CNS involvement leads to progressive drowsiness and seizures.

Diagnosis

The triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure preceded by bloody diarrhea by 5–10 days strongly suggests a diagnosis of HUS. Differential diagnosis is from other causes of acute renal failure, especially those with microangiopathic anemia such as lupus and malignant hypertension. An entity that may present with all the manifestations of HUS is bilateral renal vein thrombosis. A noteworthy distinguishing feature of this condition is remarkable enlargement of the kidneys.

Complications

These include:

- Gross anemia, acidosis, hyperkalemia, overhydration, CCF, hypertension and uremia.
- Central nervous system—seizures and coma
- Gastrointestinal tract—colitis
- Endocrine—diabetes mellitus
- Rhabdomyolysis.

Treatment

Aggressive therapy of acute renal failure leads to survival of almost 90% subjects with HUS. Gratifying results have been obtained with high dose intravenous immunoglobulin therapy (IVIG). Various other therapies like steroids, heparin, platelet inhibitors, fibrinolytic therapy, plasma-pheresis, fresh frozen plasma, etc. have been tried, but are of doubtful value.

626 NEPHROTIC SYNDROME

Nephrotic syndrome (NS) is a common pediatric problem, a vast majority of cases belonging to the age group 2–6 years.

Definition

It is characterized by massive proteinuria (albuminuria), hypoproteinemic edema and hypercholesterolemia (hyperlipidemia). Because of gross proteinuria ($>1 \text{ g/m}^2/\text{day}$), serum albumin is low ($<2.5 \text{ g/dL}$). Blood pressure and blood urea are usually normal.

Etiopathogenesis

Three types are known:

- **Idiopathic NS:** In childhood, the vast majority (90%) belongs to this category. It is regarded by many authorities as a sort of **autoimmune phenomenon**, especially since it responds well to immunosuppressive therapy. Idiopathic NS is of two types:
 1. **Minimal change NS (MCNS):** This is the predominant type, seen 85% of the cases.
 2. **Significant change NS (SCNS):** This is infrequent. Mesangial proliferation is seen in 5% cases and focal sclerosis in 10% of cases.
- **Secondary NS:** Unlike adults, children only occasionally suffer from this type. It is responsible for only 10% of overall nephrotic children. The disease in this case is usually mediated by some form of glomerulonephritis (the dominant being membranous and membranoproliferative forms). Its known causes are listed in (Box 31.11).
- **Congenital NS:** It is a serious, but rare condition associated with congenital anomalies of renal architecture, presenting in first 3 months of life with anasarca, hypoalbuminemia and oliguria. Two types are recognized (Box 31.12). Therapy is only supportive. Death occurs in infancy, usually due to severe renal insufficiency or overwhelming infection.
- **Infantile NS:** The term is applied to NS occurring in infants between 4–12 month of age. Its major causes are:
 - NPHS2 mutations
 - Diffuse mesangial scleroses (DMS).

Relative Incidence of Types of NS

About 80–85% of children with NS are of minimal lesion, or corticosteroid responsive type. The term, **minimal change nephrotic syndrome** (MCNS) is currently considered most appropriate for this condition. The rest of the 15–20% cases of NS are due to chronic glomerulonephritis and other renal diseases, including those secondary to systemic disorders.

STEROID-SENSITIVE/RESPONSIVE NEPHROTIC SYNDROME

(Idiopathic Nephrotic Syndrome, Minimal Change Nephrotic Syndrome)

As already emphasized, around 80–85% children with NS belong to this type.

Box 31.11 Etiology of secondary nephrotic syndrome

Chronic glomerulonephritis

- Focal glomerulonephritis
- Membranous glomerulonephritis
- Membranoproliferative glomerulonephritis
- Mesangial proliferative glomerulonephritis
 - With IgM deposition
 - With IgA-IgG deposition (Berger disease).

Connective tissue disorders

- SLE
- HSP
- Rheumatoid arthritis.

Metabolic disorders

- Diabetes mellitus
- Amyloidosis.

Infections

- **Malaria:** *P. malariae* infections
- **TORCH:** Syphilis, Toxoplasmosis, Hepatitis B and C, Varicella, HIV-1
- Infective endocarditis
- HIV-1/AIDS.

Cardiovascular

- Malignant hypertension
- Infective endocarditis
- Sickle-cell disease
- Renal vein thrombosis*.

Malignancies

- Lymphomas
- Leukemias.

Drugs

- Heavy metals—Mercurials, gold salts, uranium, penicillamine,
- NSAIDs
- Aminoglycosides
- Anticonvulsant: Trimethadione
- **ADRs**—Penicillin hypersensitivity, captopril, heroin, lithium, interferon
- Immunological/allergic disorders
 - Bee sting
 - Food allergens.

Miscellaneous

Ventriculoatrial shunt infection.

Abbreviations: SLE, systemic lupus erythematosus; HSP, Henoch-schönlein purpura; TORCH, toxoplasmosis, other agents, rubella, cytomegalovirus and herpes simplex; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; ADR, adverse drug reaction.

* Recently, reports have appeared suggesting that renal vein thrombosis may well be a consequence rather than a cause of nephrotic syndrome.

Box 31.12 Etiologic types of congenital nephrotic syndrome

Gene Mutations (Primary type)

- Finnish type (nephropin Mutations in NPHS1 gene)
- Podocin gene mutation NPHS2
- WTI gene mutation (Denys-Drash syndrome)
- PLCE1 gene mutation
- LMX1B gene mutation (Nail patella syndrome)
- LAMB2 gene mutation (Pierson syndrome).

Infections (Secondary type)

TORCH infection-associated.

Abbreviations: WT, Wilms' tumor; LAMB2, Laminin beta2; NPHS, nephropin; TORCH, toxoplasmosis, other agents, rubella cytomegalovirus and herpes simplex virus.

Pathology

The essential lesion is the thickening of the foot processes (podocytes) of the basement membrane. As a result, there is increased permeability of glomerulus to plasma proteins. It is now convincingly demonstrated by immunodiffusion technique that proteins of low molecular weight are filtered by the glomeruli more easily than those of high molecular weight. Thus, in minimal lesion, only albumin is filtered. If, however, the damage to basement membrane is significant, it results in escape of large proteins such as globulins as well. This may be interpreted to mean that severity of NS can be judged from the **selective proteinuria** which is expressed as **selective permeability index**. In advanced cases, the index exceeds 0.2.

Clinical Features

Most patients are between 2 and 6 years at the onset of NS. Male to female ratio is around 2:1. The onset is usually gradual (insidious), but may be acute in some cases. A previously well child begins to gain weight over a period of days to weeks. This may be accompanied by periorbital puffiness (Fig. 31.4). All this may be regarded by the parents as a sign of health until obvious swelling of the body results. In a well-developed case, the clinical picture is fairly consistent—a preschooler having massive anasarca (Fig. 31.5) involving the face, extremities, trunk, abdomen (ascites) and genitalia, especially marked scrotal edema almost resembling hydrocele (Fig. 31.6). At times, hydrothorax may be present. This as well as massive ascites may cause respiratory embarrassment. Also, waterlogging may cause edema of the gut and diarrhea. Some enlargement of the liver is usual.

Blood pressure may be slightly raised in an occasional case. Anemia may be associated. ESR is usually high. Urine output is reduced. Superadded infections of respiratory tract, skin (cellulitis) and peritoneum (peritonitis) occur due to reduction in immunoglobulins. Infection may act as a precipitating factor for the relapse of NS.



Fig. 31.4: Nephrotic syndrome. Note gross periorbital and facial edema.



Fig. 31.5: Nephrotic syndrome. Note generalized edema (anasarca).



Fig. 31.6: Nephrotic syndrome: Note generalized edema, including hydrocele and involvement of the penis.

Diagnosis

In most cases, clinical picture is so characteristic that diagnosis is quite clear. Occasionally, acute glomerulonephritis, kwashiorkor, anemia with hypoproteinemia or CCF may need to be differentiated. Box 31.13 gives causes of proteinuria (other than NS). The following laboratory investigations are of value:

- **Urine:** Urine examination shows heavy proteinuria varying from 3–4 plus; at 24-hour urine protein varies from 2–20 g/24 hours. Estimation of selective permeability index helps to find out how advanced the disease is. Transient slight hematuria may be present in some cases.
- **Blood:** Hypoproteinemia, predominantly hypoalbuminemia (below 2.5 g), is remarkable. Serum albumin/globulin ratio is reversed. There is also hypogammaglobulinemia with an increase in the lipoproteins, i.e. alpha-2 and beta-globulins.

Box 31.13 Conditions other than nephrotic syndrome figuring in differential diagnosis of proteinuria

Benign

- Febrile proteinuria (transient)
- Exercise proteinuria (transient)
- Postural (orthostatic) proteinuria.

Pathologic

- Tubular
 - Hereditary
 - Lowe syndrome
 - Cystinosis
 - Wilson disease
 - Proximal renal tubular acidosis.
 - Acquired
 - Vitamin D intoxication
 - Analgesic abuse
 - Hypokalemia
 - Antibiotics
 - Metals (mercury, gold, lead)
 - Penicillamine
 - Cystic disease
 - Sarcoidosis
 - Acute tubular necrosis
 - Interstitial nephritis
 - Homograft rejection.
- Glomerular
 - Persistent asymptomatic proteinuria.

Box 31.14 Indications for kidney biopsy

At onset

- Age less than 1 year
- Gross hematuria, persistent microscopic hematuria or low serum C_3
- Sustained hypertension
- Renal failure not attributable to hypovolemia
- Suspected secondary causes of NS.

After initial treatment

- Proteinuria persisting despite 4 weeks of daily steroid therapy—steroid-resistant NS
- Before treatment with cyclosporin A or tacrolimus.

Abbreviation: NS, nephrotic syndrome.

- Serum cholesterol and triglyceride levels show moderate to gross increase.
- Creatinine clearance is low.
- Blood urea nitrogen is often slightly increased.
- Hypomagnesemia is generally present.
- ASO titer is low in a large majority of the cases.
- Serum IgG is raised, IgM low and IgE raised.
- Serum complement (C_3 and C_4) is normal.

- **Kidney biopsy:** Percutaneous kidney biopsy is a useful measure for exact diagnosis as well as for assessment of prognosis. The procedure is detailed in Chapter 49 (Pediatric Practical Procedures). Indications for doing biopsy are listed in Box 31.14.

Treatment

First Attack

Corticosteroids constitute the cornerstone of management. Various schedules have been employed. Generally, prednisolone, (2 mg/kg/day) in divided doses, is most appropri-

Box 31.15 ADRs of chronic steroid therapy

- **Electrolytes:** Fluid retention (edema), hypokalemia
- **Disfiguring:** Round facial contour, cervicodorsal hump (buffalo), anterocervical hump (Turkey) and pigmentation, hirsutism, baldness and kyphosis
- **Disquieting:** Muscle wasting, hypertension, glycosuria and menstrual disturbances
- **Enjoyable:** Euphoria, increased appetite
- **Disturbing:** Insomnia, polyuria, headache, thinning of skin with development of striae and bruising, myopathy and poor wound healing
- **Alarming:** Epigastric discomfort, intercurrent infections, osteoporosis and psychosis.

Abbreviation: ADR, adverse drug reaction.

ate. Once edema has completely disappeared and the child has no albuminuria (this takes about 6 weeks), maintenance therapy can be given. For this purpose, prednisolone is given in a dose of (1.5 mg/kg/day) as a single morning administration on every alternate day, for another 6 weeks. Then, it is tapered off, or abruptly stopped as per new trend.

Occasionally, a subject who responds to daily prednisolone initially may suffer from a relapse shortly after he is shifted to or after stopping alternate day therapy. This is termed **steroid dependence**. During steroid therapy, development of Cushingoid facies frequent. A check on complications such as hypertension is essential. Remaining complications caused by prolonged steroid therapy include posterior subcapsular cataract, poor glucose tolerance, emotional problems and growth retardation (Box 31.15).

Steroid therapy leads to necessary diuresis by 10–14 days. But if it takes considerable time and there is much respiratory and cardiac embarrassment as a result of water-logging, large doses of diuretics like furosemide may be given for a short period. It is advisable to give spironolactone (an aldosterone antagonist) also else, during the diuretic phase, potassium supplements should be added. Occasionally, tapping of the ascites and thoracentesis may be needed.

Antibiotics should be given in the presence of an infection. Their prophylactic use is not recommended. Diet should be normal. There is no logic in limiting the protein intake. Salt and fluid restrictions are helpful when the child is in an edema phase. Albumin infusion, 1g/kg/day, in 8–12 hours, may be given as an adjunct in subjects with massive edema, particularly when accompanied by ascites and pleural effusion. It must always be followed by IV furosemide. Negative points of such a therapy are:

- Expensiveness
- Results are only transient
- Risk of hypertension, circulatory overload and pulmonary edema since edema fluid is mobilized into intravascular compartment. General measures include adequate rest, good nursing, training the child and/or family members regarding urine testing for albumin and reassurance to the parents. The pediatrician should educate the family about the important aspects of the disease which is known to have a prolonged course.

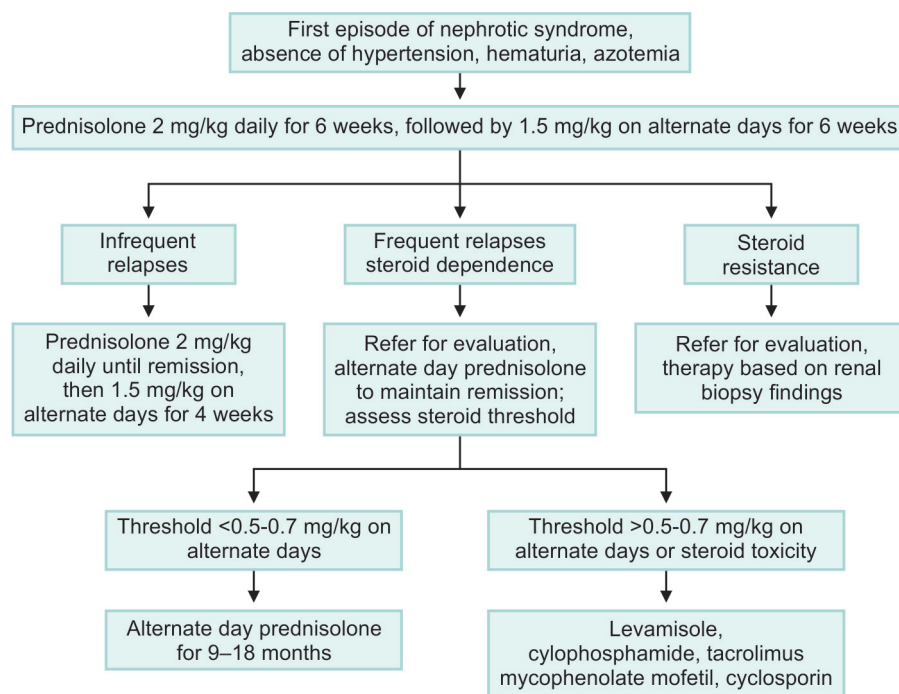


Fig. 31.7: Algorithmic approach to management of patients with steroid sensitive nephrotic syndrome.

Relapse

In case of a relapse (reappearance of edema and proteinuria, usually triggered by an infection), give prednisolone (2 mg/kg/day) in 3–4 divided doses until proteinuria disappears (usually it does not take more than 2 weeks) followed by 1.5 mg/kg, as a single morning dose for another 4 weeks.

- **Infrequent relapses:** This approach is applicable for subsequent relapses provided these are “infrequent” (3 or less in a year).
- **Frequent relapses/steroid dependent:** In case of frequent relapses (3 or more year), child should be treated with long-term alternate day regimen for 9–18 months. Prednisolone dose should be smaller but enough to keep the child free of proteinuria as well as side-effects. A short course (8–12 weeks) of steroid sparing agents (levamisole, cyclophosphamide, tacrolimus, mycophenolate mofetil, rituximab or cyclosporine) is indicated in subjects who show frequent relapses or who are steroid dependent.

STEROID-RESISTANT NEPHROTIC SYNDROME

(Secondary Nephrotic Syndrome)

Steroid resistant NS is defined as “no remission in spite of treatment with adequate dose of prednisolone (2 mg/kg/day; 60 mg/m²/day) over a span of 4 weeks”. For steroid resistance, kidney biopsy dictates the therapeutic approach. But, it is the patient’s response to therapy rather than the renal histology that predicts the renal outcome. Drugs employed include:

- **Calcineurin inhibitors:** Cyclosporine, tacrolimus
- **Cyclophosphamide:** Both oral and IV
- Methylprednisolone
- Prednisolone (high dose) with cyclophosphamide.

Fig. 31.7 presents an algorithmic approach to management of NS. Fig. 31.8 presents an algorithmic approach to management of edema in NS. Finally, renal transplantation is indicated in end-stage renal failure because of steroid-resistant glomerulosclerosis (focal and segmental).

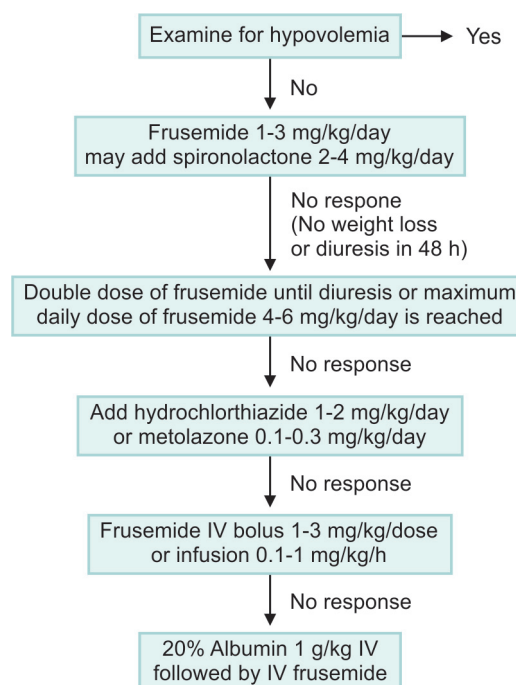


Fig. 31.8: Algorithmic approach to management of edema in nephrotic syndrome. Patients requiring high dose furosemide or addition of other diuretics should be under close supervision, preferably in a hospital. Monitoring of serum electrolytes is necessary in all patients receiving diuretics. Patients showing hypokalemia require potassium supplements or co-administration of spironolactone. The medications are reduced stepwise once diuresis ensues

Box 31.16 Factors contributing to high incidence of infection in nephrotic syndrome

- Reduced immunoglobulin levels
- Edema fluid acting as a culture medium
- Severe protein deficiency
- Reduced bactericidal activity of leucocytes
- Reduced perfusion of spleen from hypovolemia
- Loss in urine of a complement factor, properdin known to opsonize some bacteria
- Immunosuppressive therapy.

Complications

These include:

- **Infections:** Cellulitis, peritonitis, UTI, pneumonia, meningitis, arthritis, osteomyelitis. The organisms responsible for infection are *Streptococcus pneumoniae* and Gram-negative bacteria. Box 31.16 lists the factors contributing to enhanced incidence of infections in NS
- Thromboembolism
- Hypertension
- Hypovolemic shock
- Acute kidney injury
- Chronic calcium and vitamin D deficiency state with symptomatic hypocalcemia (tetany) and/or rickets/osteomalacia
- Protein energy malnutrition
- Growth retardation is a well-known accompaniment of prolonged steroid therapy. Nevertheless, catch-up growth occurs when steroid therapy is discontinued.

Prognosis

With the steroid therapy, about 80% of the children recover. Around 10–15% go into chronic renal failure. Recurrent infections (peritonitis in particular) pose a significant problem. A cumulative mortality of 2–4% occurs in MCNS. The responsible factors usually are fulminant infection or abnormalities of coagulation or circulation. That MCNS usually shows permanent remission or diminution in relapses during puberty is a myth.

RENAL OSTEODYSTROPHY (Renal or Uremic Rickets, Renal Dwarfism)

Definition

This term refers to skeletal changes that may develop in chronic renal disease characterized by chronic glomerular failure with uremia, e.g., bilateral renal hypoplasia, hydronephrosis, polycystic disease, chronic pyelonephritis.

The bony changes are related to abnormalities in mineral and bone metabolism such as malabsorption of calcium, overactivity of parathyroid glands, cutaneous vascular and visceral calcification and poor production of biologically active vitamin D by the kidneys. In preschool children with osteodystrophy, congenital malformations of the kidney are the leading cause.

Clinical Features

- Growth failure, dwarfism, wasting, muscle weakness, bone pain, bone deformities, slipped femoral epiphysis,



Fig 31.9: Renal osteodystrophy. Note the severe knock knee deformity and mottling of skin around knees in a child with chronic renal failure.

ses, pathological metaphyseal fractures, metastatic calcification, pruritus and mottling of skin around knees and thighs.

- Signs of rickets (say, widened epiphyses, frontal bossing, costochondral beading, genu varum/valgum (Fig. 31.9) and dental abnormalities, etc.) become evident in young children.
- Despite hypocalcemia, overt tetany is rare.

Diagnosis

Biochemical investigations show high blood urea, low plasma CO₂ content (usually below 20 mmol/L), blood pH below 7.38, high alkaline phosphatase, and slightly low calcium but high phosphorus so that Ca P product is elevated. Radiology shows periosteal erosions in middle and distal phalanges, distal clavicle and inner aspect of distal femur and proximal tibia.

Treatment

It consists of administering high doses of vitamin D, controlling hyperphosphatemia by administering aluminum carbonate gel and supplying oral calcium. Undoubtedly, the basic etiologic condition also needs to be attended to for lasting results. Also See Chapter 14 (Vitamins).

END-STAGE RENAL DISEASE (ESRD)

Though the exact magnitude of the problem of ESRD in India is not clear, the incidence in Western child population is 3/million/year.

Etiology

The causes may be:

- **Preventable (uncommon):** Usually diagnosed late, and
- **Unpreventable (common):** Congenital anomalies, renal dysplasia with obstructive uropathy and various forms of persistent glomerulonephritis.

Modalities of Treatment

These include:

- Chronic hemodialysis
- Chronic peritoneal dialysis—continuous ambulatory peritoneal dialysis (CAPD) or continuous cycling peritoneal dialysis (CCPD)
- Renal transplantation.

Continuous ambulatory peritoneal dialyses consists of dialysis across the peritoneal membrane and removes surplus body water through an osmotic gradient caused by the glucose concentration in the dialysate and the wastes by diffusion from the peritoneal capillaries into the dialysate. Though less efficient than hemodialysis, CAPD provides satisfactory BUN and creatinine levels. **CCPD** provides exchanges at night rather than during the day (as the patient is sleeping) by an automatic machine, thereby reducing the risk of parental fatigue and a burnout and allowing uninterrupted day of activities.

Renal transplant is the eventual goal in end-stage renal failure/disease. It may be carried out using cadaver or living related donor as source for the organ graft. In sophisticated centers in the West, it has been carried out even in infants as small as weighing a sheer 5 kg. Success rate in children over 5 years of age is as high as in adults.

Graft rejection is a major problem. With the employment of antilymphocytic globulin and cyclosporine A, and OKT 3, immunosuppressive management has considerably improved and acute graft rejection curtailed.

Undoubtedly, further advances are warranted to prevent graft rejection and thus improve the success rate of renal transplant.

ENURESIS

(Bedwetting)

Full bladder control (day and night) is attained by an overwhelming majority of children (80–90%) by the age of 5 years. Nearly all the rest of them do so by adolescence. Only 0.1–5% may fail to develop complete continence. Failure on the part of the child to gain complete continence by 5 years of age, resulting in almost total evacuation of the bladder at day time, at night (during sleep) or both is termed **enuresis**. For details See Chapter 6 (Developmental, Behavioral and Psychiatric Disorders).

SURGICAL GENITOURINARY PROBLEMS

Details relevant to the needs of the pediatric scholars are available in See Chapter 46 (Pediatric Surgery).

Multiple Choice Questions

1. Spot the wrong observation:
 - A. Renal function after birth continues to improve until it approaches adult level by the end of 2 years
 - B. Normal blood level of creatinine is: under 6 years; 0.2–0.05 mg/dL, above 6 years; 0.4–0.8 mg/dL
 - C. Infantile polycystic disease of kidneys is inherited as an autosomal dominant disease whereas adult type is inherited as an autosomal recessive disease
 - D. Horse-shoe kidney carries 2–8 times higher risk of developing Wilms' tumor
 - E. Standard treatment for phimosis is circumcision
2. All are true about nephrotic syndrome, except:
 - A. Though hypertension is not an essential feature, most cases have it
 - B. Most cases belong to the "idiopathic" type with overwhelming predominance of minimal change lesion
 - C. In minimal change lesion, classical lesion is in the form of thickening of the foot processes (podocytes) of the basement membrane
 - D. It is advisable to rule out tuberculosis before starting steroid therapy which may reactivate a dormant tuberculous focus
 - E. Secondary disease is infrequent in children
3. Each of the following statements are correct, except:
 - A. All children with acute glomerulonephritis should receive penicillin or an allied drug during acute phase
 - B. Benign proteinuria with urine protein never exceeding 1 g/24 hours may be orthostatic, febrile or exercise-induced
 - C. Among the causative bacteria, *E. coli* is the most common
 - D. Nephrogenic diabetes insipidus is characterized by failure of kidneys to respond to antidiuretic hormone (ADH) though levels of hormone is quite high
 - E. Acute kidney injury is the new nomenclature for acute renal failure
4. All the following are true for hemolytic-uremic syndrome, except:
 - A. A triad of microangiopathic hemolytic anemia, thrombocytopenia and acute kidney injury
 - B. Most cases in India are associated with acute shigellosis in the form of bloody diarrhea or simple gastroenteritis
 - C. Endothelial cell injury is the hallmark
 - D. Extrarenal complications include CNS manifestations, colitis, diabetes mellitus and rhabdomyolysis
 - E. A self-limited condition
5. Pick up the correct statement:
 - A. Renal osteodystrophy is the most important complication of nephritic syndrome
 - B. Renal transplant is the eventual goal in end-stage renal disease (ESRD)
 - C. The only special vaccine recommended in nephritic syndrome is Hib
 - D. Muscle cramps and carpopedal spasm are the only known manifestations of Bartter syndrome
 - E. Gross hematuria originating from kidneys gives urine bright red or pink color

Answers

1. C 2. A 3. A 4. E 5. B

Clinical Problem-solving

Review 1

A 4-year-old presents with massive hypoproteinemic edema, massive hypoproteinemia and hypercholesterolemia. He responds to standard therapy with prednisolone (2 mg/kg/day daily for 6 weeks and then 1.5 mg/kg/day on alternate days for another 6 weeks). However, within few days of stopping steroids, relapse occurs. The same story is repeated in the subsequent months. With three such steroid courses, he looks Cushingoid.

1. What is the diagnosis?
2. What should be the next step in such a case?
3. What are likely iatrogenic complications other than Cushingoid features in such a case?

Review 2

A 6-month-old boy suffers from poor weight gain, mild fever without any evident infection, polyuria, and episodes of dehydration in spite of excessive intake of water since 2 months of age. Investigations show serum sodium 165 mg/dL, low urine sodium, urine osmolarity 145 mOsm with no rise following desmopressin.

1. Your clinical impression?
2. What is the closest differential diagnosis?
3. What is the therapy?

Answers

Review 1

1. Steroid-dependent nephrotic syndrome.
2. The next course of therapy in steroid dependent cases should be levamisole plus decreasing doses of prednisolone on alternate days for 3–6 months. Levamisole is, however continued for at least 1–2 years. Alternatives to levamisole are cyclophosphamide, cyclosporine and mycophenolate mofetil.
3. Apart from Cushingoid appearance, chronic steroid therapy may cause hypertension, osteoporosis, subcapsular cataracts, psychosis, etc.

Review 2

1. Nephrogenic diabetes insipidus.
2. Central diabetes insipidus in which urine osmolarity rises after desmopressin administration.
3. Therapy comprises increased fluid intake, sodium restriction, hydrochlorothiazide, amiloride and indomethacin.

FURTHER READING

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DEVELOPMENTAL ASPECTS OF HEMATOPOIETIC SYSTEM

An extremely high rate of somatic growth in the fetus, relatively low oxygen tension and yet high metabolic rates of fetal tissues and sterile intra-amniotic environments necessitate the following vital features of fetal life:

- A remarkable increase in red cell mass with regulation of erythrocyte production by the hormone, erythropoietin, which is produced in the liver of the fetus, but by the kidney postnatally.
- An easy system of oxygen delivery in the form of fetal hemoglobin (HbF) which is 90% at 6 months of gestation, and 70% at term. By 6–12 months postnatally only a trace is left (maximum 1–2%). Throughout fetal life and early childhood, an inverse relationship exists between HbF and HbA as also between alpha and beta chains (switch mechanism). HbA₂ is 1% at birth, but by first birthday rises to 2.4–3.4%, the normal adult range. The ratio 30:1 of HbA: HbA₂ is maintained throughout life. High HbA₂ is found in beta-thalassemia trait and vitamin B₁₂ deficiency megaloblastic anemia. In iron deficiency anemia, HbA₂ level is decreased.
- A low demand for neutrophils so much and so that neutrophils are virtually absent in the first and second trimesters fetus. Upregulation of neutrophil production is primarily controlled by granulocyte colony stimulating factor (G-CSF) both in fetus and postnatally. The G-CSF, the principle neutrophil regulatory growth factor, is relatively lacking until 22–24th weeks of gestation. Hence, there is no or very little granulocytopoiesis. Neonates born extremely preterm run the serious risk of bacterial infections.

Unlike the blood concentration of red cells and granulocytes, platelet concentration remains constant between 150,000–450,000/mm³ from 18 weeks of intrauterine life onward. These are produced following clonal maturation of committed progenitors, colony forming units-megakaryocytes (CFU-Meg) into megakaryoblasts and then megakaryocytes. Table 32.1 gives the average hematologic values in pediatric subjects, including adolescents.

ANEMIAS

Definition

Anemia is to be defined as reduction in hemoglobin concentration, hematocrit or red cell mass. Cut-off point for defining anemia at different age groups as per Table 32.2.

Table 32.1: Average hematologic values in neonates, infants, children and adolescents

Ages	Hb (g/dL)	PCV (%)	Retics (%)	TRCC (10 ¹² /L)	TLC (10 ⁹ /L)	PMN (%)
Neonates						
At birth	16.8	55	5.0	4.8	18.0	61
1–3 days	18.8	57	4.0	5.3	18.9	61
7 days	17.8	55	1.0	5.1	12.2	45
14 days	16.5	51	1.0	4.9	11.9	40
1 month	14.0	43	1.0	4.2	10.8	35
Infants						
3 months	11.5	35	1.0	3.8	10.8	36
6 months	11.5	35	1.0	3.8	11.8	32
1 year	12.0	36	1.0	4.5	11.5	31
Children						
2–6 years	12.5	37	1.0	4.6	9.0	42
6–12 years	13.5	40	1.0	4.6	8.5	55
Adolescents						
Boys	16.0	43	1.0	4.9	8.1	55
Girls	14.0	41	1.6	4.6	8.1	55

Abbreviations: Hb, hemoglobin; PCV, packed cell volume; TRCC, total reticulocyte count; TLC, total leukocyte count; PMN, polymorphonuclear leukocytes.

Table 32.2: Cut-off point for defining anemia at different age groups

Age group	Hemoglobin
Under 2 weeks	13 g/dL
Upto 6 months	9.5 g/dL
6 months–6 years	11 g/dL
6 years–14 years	12 g/dL
Above 14 years (Boys)	13 g/dL
Above 14 years (Girls)	12 g/dL
Pregnant women/adolescents	11 g/dL

Grading

World Health Organization (WHO) grades anemia according to Hb level as given in Table 32.3 and Table 32.4 gives clinical grading of anemia.

Classification of Anemias

Conventionally, anemia's have been classified on the basis of etiology and red blood cells (RBC) morphology. Box 32.1 describes a classification of anemia based on etiology and pathogenesis.

Table 32.3: WHO grading of anemia

Hemoglobin levels	Grades
Between 10 g/dL and cutoff point for age	Mild
Hb between 7 g/dL and 10 g/dL	Moderate
Hb under 7 g/dL	Severe

Abbreviations: WHO, World Health Organization; Hb, hemoglobin.

Table 32.4: Clinical grading of anemia

Clinical observation(s)	Grades
Pallor restricting itself to only conjunctiva and/or mucous membrane	Mild
Obvious skin pallor and appendages	Moderate
Whitening of palmar creases	Severe

Box 32.1 Classification of anemia**Disorders of impaired RBC production**

- Deficiency anemia
 - Iron deficiency anemia
 - Nutritional megaloblastic anemia (B_{12} and folate deficiency)
 - Mixed deficiency states (dimorphic anemia)
- Bone marrow failure
 - Aplastic anemia:** Congenital and acquired (idiopathic and secondary)
 - Selective red cell aplasia:** Congenital, Diamond-Blackfan anemia and acquired, e.g. transient erythroblastopenia of childhood
 - Marrow replacement:** Myelofibrosis, osteopetrosis and malignancies
- Impaired erythropoietin production
 - Chronic renal failure
 - Hypothyroidism and hypopituitarism
 - Chronic malnutrition
- Miscellaneous
 - Congenital dyserythropoietic anemias.
 - Erythropoietic porphyria

Disorders of increased RBC destruction

- RBC membrane defect, e.g. hereditary spherocytosis
- Defects of hemoglobin synthesis
 - Quantitative (Thalassemias), e.g. beta, alpha, delta-beta thalassemias
 - Qualitative (Hemoglobinopathies), e.g. sickle cell disease, HbE disease etc.
 - Combined—Quantitative and qualitative defects, e.g. HbS-beta thalassemia.
- Defects of RBC enzymes:** G6PD deficiency, pyruvate kinase deficiency
- Acquired defects
 - Immune hemolysis—warm and cold antibody type, ABO and Rh-incompatibility.
 - Infections—malaria, kala-azar, acute bacterial infections.

Abbreviations: RBC, red blood cells; G6PD, glucose 6 phosphate dehydrogenase; HbE, hemoglobin E; RH, rhesus; HbS, hemoglobin S.

NUTRITIONAL ANEMIAS

In practice, nutritional anemia, particularly due to iron deficiency, virtually dominates the scene. Prevalence of nutritional anemia in Indian children is almost of epidemic proportion—a public health problem indeed.

* A healthy fullterm baby has iron stores that are enough for first 6 months. This is said to be true even if the mother has had anemia during pregnancy. This has earned the fetus the title of a 'merciless parasite' who does not excuse the kind host either.

** Cow milk protein hypersensitivity may cause GI bleed and, thereby, IDA. Moreover, cow milk is not only deficient in iron content, its iron is of low bioavailability. Furthermore, its higher calcium content competes with iron for absorption.

*** Some hepatomegaly may also coexist.

IRON DEFICIENCY ANEMIA (IDA)

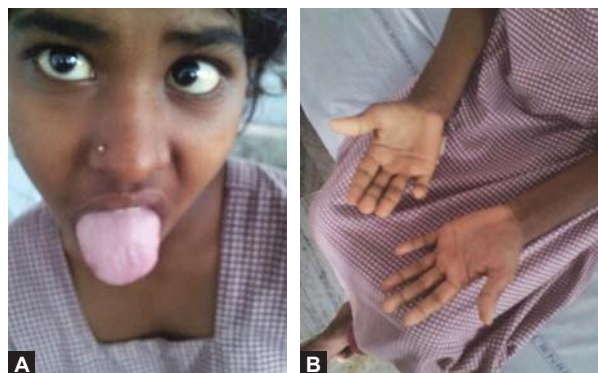
Iron deficiency is the most common etiologic factor in anemias. It is especially common in infancy because both breasts as well as cow milk do not provide the baby's needs for iron. Secondly, poor iron stores in premature babies* predispose to further deficiency so that, at about third month (the time for maximal physiologic reduction of hemoglobin), there may be marked IDA. Twins commonly become iron deficient. At times, only one of them may suffer. Preschool age and adolescence are particularly more vulnerable for IDA because of rapid somatic growth.

In older children, the causes include inadequate intake, malabsorption, infection, chronic blood loss (ancylostomiasis) and cow milk protein (CMP) hypersensitivity**. Recently, convincing evidence has accumulated to the effect that iron deficiency may *per se* cause an absorptive defect by damaging the small intestinal epithelium.

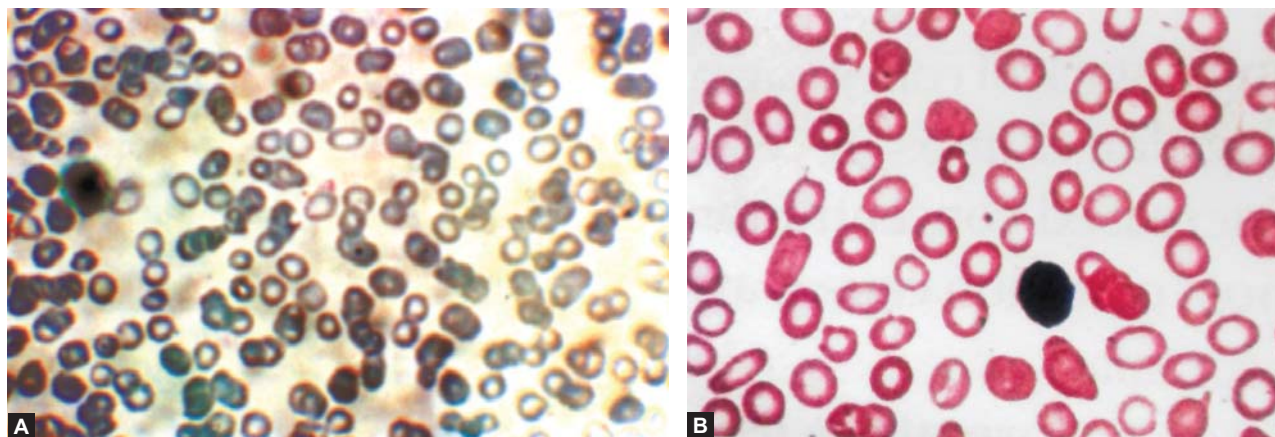
Rarely, in error of iron metabolism such as sideroblastic anemia, idiopathic pulmonary hemosiderosis and congenital transferrin deficiency, iron gets stored in the body rather than being utilized for erythropoiesis.

Clinical Features

- Progressive pallor, irritability, anorexia, tiredness, weakness, cramps, breathlessness, tachycardia, failure to thrive (FTT), atrophy of tongue papillae (Fig. 32.1A), glossitis, angular stomatis, cheilosis, pica and koilonychia/Platonychia. With progression of anemia, pallor of palms becomes pronounced with near whitening of palmar creases in severe anemia (Fig. 32.1B).
- Diarrhea is often present.
- At times, pseudotumor cerebri may occur.
- Occasionally, especially in severe anemia, spleen*** is enlarged.
- Hemic murmur (soft systolic, having maximal intensity over the base and changing with position) is common.



Figs 32.1A and B: Iron deficiency anemia. (A) Smooth tongue with loss of papillae, most marked along the edges; **(B)** Marked pallor of palm (mark the remarkable change in color compared to arms) with whitening of creases.



Figs 32.2A and B: Iron deficiency anemia. (A) Peripheral blood film showing microcytic-hypochromic picture with anisocytosis and poikilocytosis; (B) Focus on microcytosis in particular. Similar picture may be seen in hemolytic anemias, sideroblastic anemia, anemia of chronic disorders and lead toxicity.

- Though most children learn to adapt anemia of prolonged duration, some may suffer from cardiomegaly and even congestive cardiac failure (CCF), particularly in the presence of an added stress.
- Low infant behavior record (IBR) as manifested by unhappiness, lack of cooperation and shorter attention span, as also lower mental development index (MDI). Even subclinical iron deficiency causes low MDI. Both IBR and MDI revert to normal following correction of iron deficiency.

Diagnosis

Diagnosis of IDA rests upon demonstration of microcytic hypochromic anemia along with reduced body/serum iron.

- Peripheral smear examination shows microcytic hypochromic RBCs with anisopoikilocytosis (Fig. 32.2) and polychromasia.
- Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) are reduced.
- Red cell distribution width (RDW), a measure of variation of red cell size is increased.
- Total RBC count is decreased.
- There is mild reticulocytosis, leucocytosis and thrombocytosis.
- Serum iron is reduced (<30 mg/dL is considered diagnostic).
- Serum ferritin is also reduced (<10 ng/mL).
- Total iron binding capacity (TIBC) is increased. TIBC over 400 mg/dL strongly suggests IDA.
- Transferrin saturation is reduced (<12–14% in children and <16% in adolescents).
- Bone marrow is hypercellular with reduced iron stores, but examination of bone marrow for diagnosis is not required.

On the basis of biochemical and hematological changes iron deficiency is graded into 3 Stages (Box 32.2).

Differential Diagnosis

IDA needs to be differentiated from anemia showing hypochromic microcytic picture, say lead poisoning, beta-

Box 32.2

Three stages of iron deficiency based on biochemical and hematological changes

1. **Stage I:** Depletion of iron stores (ferritin is decreased, transferrin saturation, serum iron and hemoglobin are normal)
2. **Stage II:** Depletion of transport iron (transferrin saturation and serum iron also reduced, Hb is normal)
3. **Stage III:** State of IDA (frank features of IDA).

Abbreviations: IDA, iron deficiency anemia; Hb, hemoglobin.

thalassemia trait, thalassemia major, Hb H disease (a type of alpha-thalassemia) and anemia accompanying chronic inflammations and infections.

Treatment

Specific Treatment

It consists of replacing the iron deficiency with iron which may be administered orally or parenterally.

Oral Therapy

The dose of elemental iron is 3–6 mg/kg/day in 3 divided doses. Any iron can be given. However, the most economic and most easily available one is the simple ferrous sulfate, containing 20% elemental iron (Table 32.5) and available as 200 mg tablets. Oral iron, in any form, causes gastric irritation if

Table 32.5: Elemental iron content of various oral iron salts

Salt	Elemental iron (%)
Ferrous sulfate	20
Anhydrous ferrous sulfate	37
Ferrous sulfate (exsiccated)	30
Ferrous fumarate	33
Ferrous fructose	25
Ferrous succinate	23
Ferrous lactate	19
Ferrous carbonate	16
Ferric ammonium citrate	15
Ferrous gluconate	12
Colloidal iron	50

636 given in excess dose. The side-effects of oral iron include nausea, vomiting, diarrhea, constipation, abdominal cramps, staining of teeth and tongue and discoloration of stools.

Even recommended dose may cause gastrointestinal tract (GIT) disturbance in which case readjustment of the dose becomes essential. For optimal absorption, iron dose should be administered in between meals. Concurrent administration of vitamin C enhances its absorption whereas foods rich in phytates (cereals) and phosphates (milk) reduce it. The total duration of treatment varies from 3–6 months. Therapy must continue in the same dose for a minimum of another 6 weeks after attainment of normal hemoglobin. Hemoglobin rise following oral iron therapy is around 0.4 g/dL/day. Factors contributing to poor response to oral iron include:

- Poor tolerance
- Subtherapeutic dose (<3–6 mg/kg/day)
- Insufficient length of treatment
- Accompanying illness—malabsorptive state (celiac disease, cystic fibrosis, tropical sprue, giardiasis) infection(s)
- Achlorhydria from coadministration of drugs such as proton pump inhibitors and H₂ blockers
- Coexistence of folic acid/vitamin B₁₂ deficiency
- Persistent bleeding (occult or frank)
- Poor compliance
- Iron administration soon after intake of milk (phosphates) or cereals (phytates)
- Incorrect diagnosis of IDA in thalassemia, lead poisoning or sideroblastic anemia.

Parenteral Therapy

It is indicated when one desires to cut down hospital stay, if oral medication is not feasible because of intolerance or presence of diarrheal disease, when GI bleeding is likely to be worsened by oral iron therapy, and when there is a sufficient reason to believe that the patient is unlikely to regularly take his pills. A small group of pediatricians prefers to initiate treatment with parenteral iron (a few injections only) and then put the patient on oral medication. They believe that such a schedule helps in tiding over the initial difficulties in management. Total dose is calculated by one of the formulas:

Dose of parenteral iron (intravenous {IV} infusion or intramuscular {IM}) is calculated as follows:

Iron required = $2.5 \times \text{body weight (kg)} \times \text{Hb deficit (g/dL)}$

(Hb deficit is the difference between measured and desired values of Hb). An additional 20–30% of the calculated dose is included to replenish the stores. Parenteral iron may be given IM or IV as shown in Box 32.3.

Blood Transfusion

It should be reserved for life-threatening situations (acute severe bleeding, CCF, before an invasive procedure) when anemia is very severe and has associated symptoms warranting a rapid rise in hemoglobin level. If a decision to give blood has been taken, transfusion must be given slowly. Danger of CCF in such patients is really high (Box 32.4). A loop diuretic (furosemide) should be adminis-

Box 32.3

Salient features of parenteral preparations of iron

IM administration

Two preparations, iron-dextran complex (Imferon) and iron-sorbitol (Jectofer) are available. Daily dose of IM injection should not exceed 5 mg/kg, i.e. 50 mg in infants and 100 mg in adolescents. The best site is upper and outer quadrant of thigh. To avoid repeat injection at the earlier prick, it should be given in Z fashion. The injection is given deep IM making sure that staining of skin does not occur. Adverse effects include local pain, fever, arthralgia, and lymphadenopathy

IV administration

Two preparations, iron dextran complex (Imferon) and iron sucrose, can be given by this route.

1. **Iron dextran complex:** After testing sensitivity with a small dose, the TDI is given in 250–500 mL of saline slowly over 6–8 hours. It is now only infrequently employed in view of the risk of shock and anaphylaxis.
2. **Iron sucrose:** This is the current choice. It is given as a single dose IV infusion. Unlike IV iron dextran complex, it is safe.

Abbreviations: IM, intramuscular; IV, intravenous; Hb, hemoglobin; TDI, total dose infusion.

Box 32.4

High-risk factors in blood transfusion in severe anemia

- Age under 2 years—poor cardiac tolerance may lead to cardiac complications especially with the presence of added stress in the form of pre-existing CCF, bronchopneumonia, congenital heart disease and edematous malnutrition, etc
- Malnutrition—myocardial weakness because of degenerative changes as in beriberi and circulatory overload as in kwashiorkor may lead to CCF
- Impending CCF
- Acidosis
- Hypoglycemia
- Stored blood.

Abbreviation: CCF, congestive cardiac failure.

tered to children with impending CCF/coexisting CCF. Ideally, a partial exchange transfusion is most appropriate in case of severe IDA accompanying CCF. Since iron is likely to cause proliferation of *Escherichia coli*, it should be avoided during the course of an infection, especially in malnourished children.

Other measures include adequate nutritional rehabilitation and adequate management of the underlying cause of anemia and associated illness. In our country, the worm infestations are invariably present and should be eradicated. Otherwise response to iron may be poor. Likewise, besides malnutrition, deficiencies of other hematopoiesis factors such as folic acid and vitamin B₁₂ (which may introduce an element of macrocytosis/megaloblastosis in children with IDA) should also receive attention.

Control Measures

- Neonates born preterm and low birth weight (LBW) should receive oral iron by 2–4 weeks of age, provided that they are infection-free.
- Exclusive breastfeeding should be given for first 6 months.

- Complimentary foods rich in iron, say green leafy vegetables, beans, pulses should be initiated at 6 months of age since exclusive milk diet is likely to contribute to development of IDA in the infant in the second half of first year.
- Periodic treatment of intestinal parasitic infestations, especially hookworm infection, is quite helpful. Walking barefooted should be avoided.
- Iron supplements for susceptible infants and children and at puberty, especially in girls. This is usually achieved with iron tablets, syrup or drops. Alternative strategies include:
 - Availability of iron-fortified salt (Government of India program) and food items.
 - Availability of Sprinkles a novel form of microencapsulated iron which can be packed in easy-to-use sachets for fortifying weaning foods at home. A low dose of 12.5 mg/day of elemental iron is not only quite effective, but also better tolerated.

ANEMIA OF PROTEIN ENERGY MALNUTRITION (PEM)

As stated in Chapter 13 (Malnutrition), anemia is a common accompaniment of PEM. Generally, it is mild to moderate. However some of the children suffering from kwashiorkor have even severe anemia. It may be of variable morphology—hypochromic microcytic, macrocytic/megaloblastic or dimorphic-reflecting vitamin, mineral and protein deficiency whereas protein lack per se can cause anemia. In clinical practice, anemia associated with PEM is seemingly multifactorial in origin. Besides, dietetic inadequacy of the nutrients needed for synthesis of hemoglobin factors such as infections and infestations and coexisting absorptive dysfunction play significant role in its etiopathogenesis (Fig. 32.3). These factors need to be tackled if prompt response is the goal. Just providing nutrients does little good.

As regards the blood transfusion in treatment of such anemia, it is only infrequently required. Overenthusiasm in this behalf may mean losing the patient. The risk of CCF is particularly high. We have seldom resorted to transfusion unless anemia is very severe (2 or 3 g/dL hemoglobin). It is given very slowly, preferably after administering a modern fast-acting diuretic like furosemide (IV) to minimize chance of precipitating CCF.

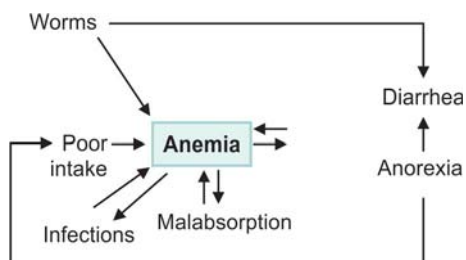


Fig. 32.3: Nutritional anemia cycle. Note the vicious cycle that is tough to break.

* Pyridoxine-responsive sideroblastic anemia due to therapy with isoniazid in tuberculosis has also been described. It responds favorably to small doses of vitamin B₆ given orally.

PHYSIOLOGICAL ANEMIA OF PREMATUREITY

Definition

Normal decline in the Hb over first few weeks of life in term infants is known as **physiologic anemia of infancy**. The fall in Hb is more in infants that born premature. This exaggerated fall in Hb is termed as **physiological anemia of prematurity**.

Etiology

The rapidity and magnitude of fall of Hb vary with the gestational age of infants and their Hb levels at birth. In term infants Hb may fall to levels as low as 9–11 g/dL by 8–12 weeks age while in premature babies, Hb as low as 8 g/dL have been reported to occur by 4–8 weeks of age.

This physiologic anemia is thought to result primarily from decrease in the red cell mass rather than hemodilution resulting from increasing plasma volume. Minimum Hb levels in infants with comparatively lower Hb at birth are observed earlier than those with higher Hb though the lowest Hb levels observed are usually same. Levels of erythropoietin are low for the degree of anemia and the bone marrow is described as having relative erythroid hypoplasia. These observations plus normal EPO dose response curve observed in these infants suggest that inadequate EPO production is the major factor in the pathogenesis of anemia of prematurity.

Treatment

On the basis of these, EPO therapy has been extensively used for treatment of these infants. Results in premature babies weighing over 1000 gms show decreased transfusion requirement, but results in those weighing less than 1000 gms have not been consistent.

HYPOCHROMIC ANEMIAS REFRACTORY TO IRON

Pyridoxine (Vitamin B₆) Dependency Anemia

This hereditary disorder*, acquired as an X-linked recessive trait, is rare. It is characterized by severe microcytic-hypochromic anemia, often early in infancy and progressive hepatosplenomegaly. There is an elevation of serum iron. Marrow shows erythroid hyperplasia with nucleated normoblasts containing iron inclusions, the so-called **sideroblasts** in abundance. There are abnormalities of tryptophan metabolism.

In a suspected case, the diagnosis should be confirmed by response of anemia to an adequate test dose (100 mg) administered parenterally. Treatment consists of regular administration of vitamin B₆. Phlebotomy may be of added value in older children.

Sideroblastic Anemia

This, usually a familial disorder, is transmitted as an X-linked recessive disorder. The defect lies in biosynthesis of hemoglobin.

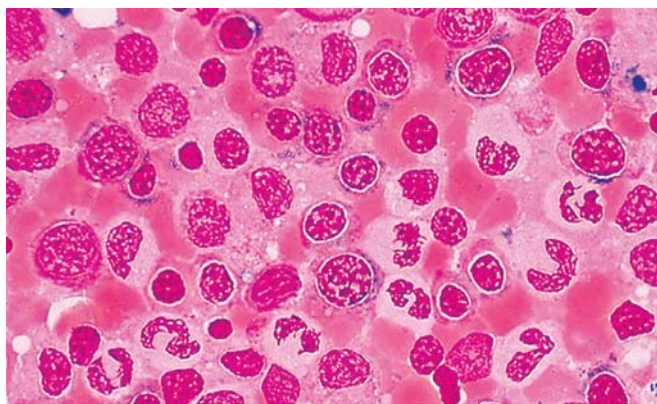


Fig. 32.4: Sideroblastic anemia. These are iron inclusions that accumulate in mitochondria around the nucleus of the RBC. Cause—failure on the part of heme to incorporate iron into it.

The anemia is characterized by iron resistance, hypochromia, elevated serum iron levels and overloaded iron stores. There are a large number of nucleated normoblasts containing iron inclusions. These are termed as **sideroblasts** (Fig. 32.4). Remember, that low concentration of sideroblasts occurs even in normal individuals. In sideroblastic anemia, there is also remarkable increase in the number of erythrocytes containing iron inclusions, the so-called **siderocytes**.

Diagnosis should be based on marrow, electrophoresis to demonstrate A_2 hemoglobin level, and therapeutic test with vitamin B_6 to differentiate it from other iron resistant hypochromic anemias.

Anemia of Infection

Chronic infections such as rheumatic fever, rheumatoid arthritis, tuberculosis and malaria may have associated mild to moderate anemia, which is normochromic or slightly hypochromic.

The mechanism of development of such anemia is not clearly understood. The operative factors include a decrease in erythropoietin, a reticuloendothelial block and slight fall in red cell survival time. Investigations show a normal marrow, presence of hemosiderin deposits and low serum iron and serum iron binding capacity. Treatment consists of giving blood transfusion, if anemia is severe and control of the infection and inflammation.

Anemia of Lead Poisoning

It usually occurs in children suffering from pica involving ingestion of flakes of lead paint, artist's paint, etc. inhalation of fumes from batteries and from practice of employing kajal or surma containing black oxide of lead into the eyes. Anemia of lead poisoning is hypochromic and microcytic and may be moderate to severe. A characteristic feature is the basophilic stippling (Fig. 32.5) of the red cells which helps to differentiate it from IDA. The level of serum iron may be low, normal or high depending on the nutritional status. Sideroblasts are, however, always present in the marrow. Moderate reticulocytosis may occur.

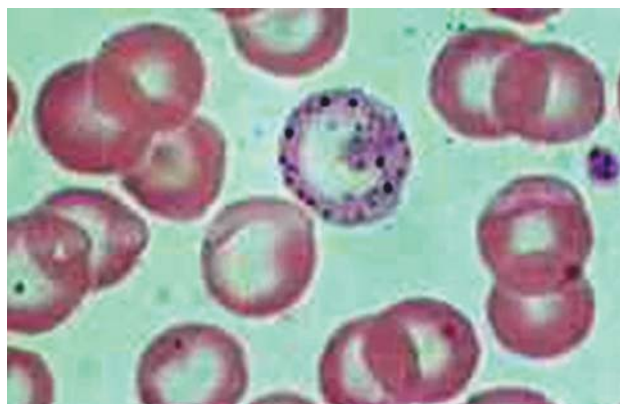


Fig. 32.5: Basophilic stippling in lead poisoning. It is not present in IDA and, therefore, assists in differentiating it from IDA. It is also seen in hemolytic anemias, megaloblastic anemias and anemias of chronic infections.

Additional diagnostic studies include urine lead level above $80 \mu\text{g/d/24 hours}$, blood lead level above $80 \mu\text{g/dL}$, markedly elevated urinary coproporphyrins or red cell aminolevulinic acid dehydratase, long bone. X-rays for lead line at the metaphyseal areas and abdominal X-ray for opaque flakes in the GIT.

Specific therapy consists of administering a combination of dimercaptopropanol (BAL) and calcium ethylenediaminetetraacetic acid (EDTA) for 2 days followed by penicillamine for 5 days. A high calcium-high phosphorus diet and massive doses of vitamin D are of value in removing lead from blood and depositing it in the bones. Severe anemia may warrant a packed cell transfusion. Iron should only be given after therapy with BAL is over.

Anemia of Thalassemia

This entity is described in details later in this very chapter.

MEGALOBLASTIC ANEMIA

Definition

Megaloblastic is defined as an anemia that is characterized by macrocytic RBCs and erythroid precursors showing erythroid dysmaturity.

Megaloblastic anemias are designated so due to a characteristic morphologic change observed in the red cell precursors in these patients. At each stage of development, the red cell precursors are larger than their normoblastic counterpart, have altered deoxyribonucleic acid (DNA) to ribonucleic acid (RNA) ratio, loose chromatin and asynchrony of nuclear and cytoplasmic maturation. Megaloblastic changes have been long recognized to occur due to deficiency of B_{12} and folic acid and in certain inherited disorders involving both micronutrients. Clinical features and usually employed hematological tests do not distinguish whether folate or B_{12} deficiency is the cause in a given case.

Etiology

It is generally held that megaloblastic anemia during infancy and early childhood is more often due to folate deficiency and

that seen among older children results from deficiency of B_{12} . However, recent evidence suggests that even B_{12} deficiency is a frequent cause of megaloblastic anemia in infants and young children. Very often deficiency of both exists.

Deficiency of B_{12}

In children in developing countries, most common cause of B_{12} deficiency is nutritional. Children born to poor, vegetarian mothers who are B_{12} deficient have poor stores at birth. If these children are exclusively fed on breast milk (which in these mothers has poor vitamin B_{12} levels) over unusually prolonged period, they develop B_{12} deficiency. Among older children, diseases of small intestine resulting in malabsorption (tropical sprue), gastritis, gastrectomy, intrinsic factor deficiency (pernicious anemia) and fish tape worm (*Diphyllobothrium latum*) infestation are other causes. Selective B_{12} malabsorption (Imerslund-Grasbeck syndrome) is also described.

Folate Deficiency

Like B_{12} deficiency, most common cause of folate deficiency is also nutritional. Maternal deficiency affecting fetus and infant is a frequent cause. Other causes include goat milk feeding, conditions with increased requirement (prematurity, chronic hemolytic anemias), malabsorptive states (tropical sprue and celiac disease), anticonvulsant therapy and antifolate drug therapy. Inherited disorders like methyl-entetrahydrofolate reductase deficiency are extremely rare.

Clinical Features

- Other than pallor, children with megaloblastic anemia have apathy, anorexia, hypotonia and developmental retardation/regression.
- Hyperpigmentation of knuckles and terminal phalanges is a common finding described in patients from Southeast Asian region.
- Glossitis with smooth, red, cracked tongue is characteristic (Fig. 32.6).
- Megaloblastic anemia being a panmyelopathy, fever due to infections resulting from neutropenia is quite common.
- Bleeding manifestations due to thrombocytopenia are observed in upto 25–30% cases.



Fig 32.6: Megaloblastic anemia. Note the atrophic tongue—smooth, red and somewhat cracked.

- Mild to moderate enlargement of liver and spleen is seen.
- Presence of bleeding and/or hepatomegaly makes them resemble acute leukemia's and bone marrow failure syndromes.
- Megaloblastic anemia is frequently seen in cases with infantile tremor syndromes.
- Neurological syndrome associated with B_{12} deficiency (subacute combined degeneration of spinal cord) is infrequent in children.

Diagnosis

- Hematological findings include low Hb and macrocytosis (Fig. 32.7A), anisocytosis, poikilocytosis and hypersegmented polymorphs on peripheral smear examination.
- Red blood cells count is low.
- Mean corpuscular volume is increased.
- Reticulocyte count is low.
- Myelopoiesis and thrombopoiesis are also affected.
- Total leukocyte count is frequently reduced.
- Platelet count is reduced.
- Pancytopenia has been seen in 40–70% cases of megaloblastic anemia.
- Bone marrow is hyperplastic with ineffective erythropoiesis and megaloblastic changes (Fig. 32.7B), as described earlier.
- Serum levels of cobalamin and folate are reduced in respective deficiency.
- Formiminoglutamic acid (FIGLU) test for folate deficiency is currently rarely done.
- Schilling test is performed to diagnose intrinsic factor deficiency.

Treatment

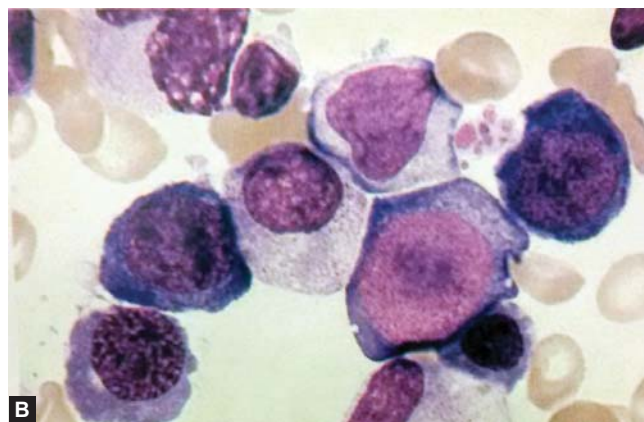
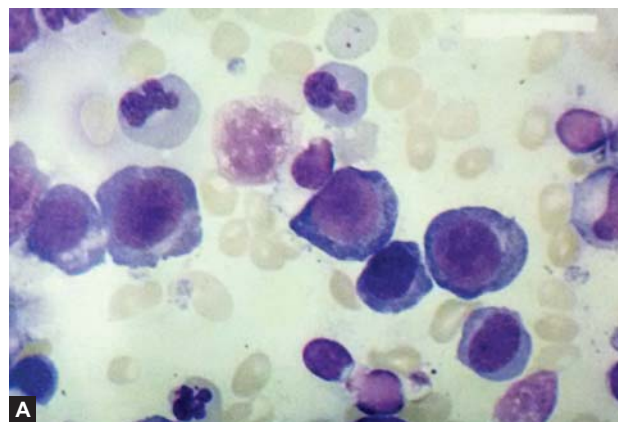
- Specific treatment is administration of folate and B_{12} in respective deficiency states.
- Folic acid in dose as small as 200–500 $\mu\text{g}/\text{day}$ may lead to adequate response, but usually dose of 5 mg orally daily is administered as this is the size of tablet available which is cheap and harmless. Therapy for 6–8 weeks or longer is usually required.
- B_{12} deficiency is usually treated with 1000 μg injection of B_{12} given one or two times per week. Tremors may occur in some patients after administration of such a large dose. Hence, 250 mg weekly for infants and 500 mg weekly for older children is a better regimen. Therapy is continued for 6–8 weeks.
- Concomitant administration of iron and correction of malnutrition is generally required.
- Underlying cause too needs to be treated.

HEMOLYTIC ANEMIAS

By the term, **hemolytic anemias**, is meant the anemias resulting from increased RBC destruction in the presence of normal or increased erythropoiesis by the bone marrow.

Characteristics of Hemolysis

Consequent upon shortened lifespan of RBCs which normally spend 100–120 days in circulation, the following indirect indicators of hemolysis may be encountered:



Figs 32.7A and B: Megaloblastic anemia. (A) Peripheral blood film showing characteristic macrocytes; (B) Bone marrow showing characteristic megaloblasts.

- Sustained reticulocytosis* (over 2%) with an unchanging hemoglobin.
- Lowering or reversal of myeloid-erythroid ratio from the normal ranges of 2:1 to 4:1.
- Expansion of medullary spaces as a result of marrow hyperplasia, leading to remarkable radiological changes, especially in skull, metacarpals and phalanges (only in chronic hemolysis).
- Raised unconjugated (indirect) serum bilirubin with negligible or slight over icterus.
- Reduced level of serum hepatoglobin since it is utilized by free hemoglobin to form large hepatoglobin-hemoglobin complex which is cleared from circulation by reticuloendothelial activity.
- Reduced serum hemopexin, another plasma protein that binds hemoglobin.
- Increased level of free hemoglobin.

Classification

Broadly speaking, hemolytic anemias may be classified into two large groups:

- **Congenital or intracorpuseular defects:** In this category, there is premature destruction resulting from intrinsic abnormalities of the red cells.
 - **Structural defects:** Hereditary spherocytosis, hemolytic elliptocytosis, paroxysmal nocturnal hemoglobinuria.
 - **Enzymatic defects:** G6PD deficiency defects in synthesis of hemoglobin. Thalassemia, sickle-cell anemia, HbC, HbD, HbE, etc, alone or in combination.
- **Acquired or extracorpuseular defects:** In this category there is hemolysis caused by noxious extra-erythrocytic factors.
 - **Immunological disorders:** Rhesus and ABO hemolytic disease of the newborn, idiopathic autoimmune hemolytic anemia, lupus, lymphoma, drug-induced (ceftriaxone, ceftibuten).
 - **Nonimmunological disorders:** Infections like malaria, clostridia; toxins like chemicals and drugs.

HEREDITARY SPHEROCYTOSIS

(Congenital Hemolytic Anemia, Congenital Acholuric Jaundice)

Etiopathogenesis

It is usually an autosomal dominant and occasionally auto-somal recessive disorder, basic defect is deficiency of spectrin, a protein lattice that maintains the stability of the erythrocyte membrane shape. As a result, the red cells become spherical and voluminous. Repeated passage through the unfavorable environments in spleen (minute apertures between the splenic cords and sinuses offer resistance to the passage of spherocyte), cause sequestration and destruction of these cells.

Clinical Features

In infancy, including neonatal period, anemia and hyperbilirubinemia may be severe enough to warrant phototherapy and/or exchange transfusion. In later months of infancy, there is a tendency for reasonable compensation. Slight icterus is usually present. The spleen may be just palpable.

After infancy, the spleen is invariably palpably enlarged. Pigmentary gallstones may develop by 4–5 years, but this event usually occurs in late childhood or adolescence. Chronic leg ulcers are infrequent in childhood. A viral infection may precipitate an aplastic crisis which should be considered a very serious complication. A transient aplastic crisis, lasting 4–6 weeks, following infection with human parovirus may occur.

Diagnosis

Anemia, hyperbilirubinemia and reticulocytosis establish the presence of hemolysis. The peripheral smear shows the characteristic spherocytic cell which is smaller than the normal red cell and is devoid of central pallor (Fig. 32.8). MCHC may be raised. Osmotic fragility is increased. There are no abnormal hemoglobin and Coombs test is negative.

* Corrected reticulocyte count = Reticulocyte count/PCV × 100.

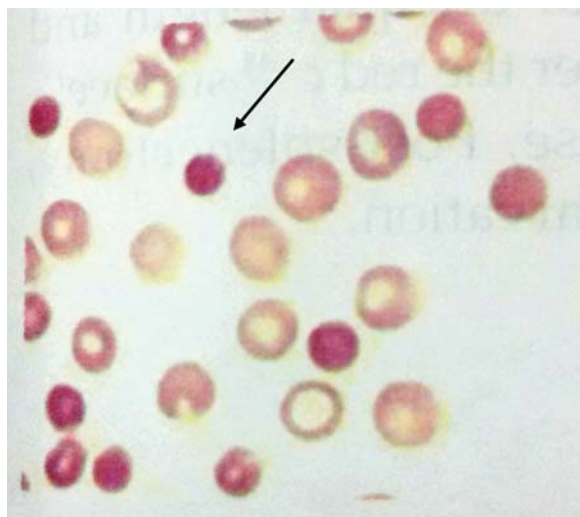


Fig. 32.8: Hereditary Spherocytosis. Note the spherocytic cell that is smaller than the normal cell and lacks central area of pallor. It may also be seen in autoimmune hemolytic anemia, recent blood transfusion, and microangiopathic hemolytic anemia.

Treatment

- Splenectomy, preferably carried out after 5–6 years of age, to safeguard against fulminant infections, leads to a clinical cure. The spherocytosis, no doubt, persists. Splenectomy also prevents occurrence of gallstones and aplastic crises, as also hemochromatosis and hepatic failure which may otherwise occur in adults.
- Prior to splenectomy, the child must receive a polyvalent pneumococcal vaccine, hemophilus influenza type b (Hib) vaccine and meningococcal vaccine.
- Administration of prophylactic penicillin in the post-splenectomy period is important to prevent against sepsis. Penicillin prophylaxis needs to continue up to early adulthood.

THALASSEMIA*

(Cooley Anemia, Mediterranean Anemia)

Thalassemia, a chronic hemolytic anemia, is an inherited disorder of adult hemoglobin synthesis which manifests as anemia with hemolytic facies, hepatosplenomegaly and skeletal changes.

Thalassemia occurs in a considerable proportion nearly all over the country. Carrier rate in different populations ranges from 2–6%. It is estimated that nearly 6000–8000 thalassemic children are born every year in India. Hence, there are over 100,000 thalassemics in the country. Table 32.6 gives prevalence of beta-thalassemia in relation to major hemoglobinopathies in the world. Thalassemia was first described by Cooley in 1925 as “a hereditary hemolytic anemia with characteristic frog-like or mongoloid facies, skeletal changes and splenomegaly”.

* Thalassemia (Greek: *thalassa* meaning sea, *emia* meaning pertaining to blood). Mediterranean Sea belt is considered its “home” though it is prevalent in Africa to South-east Asia.

** Fetal hemoglobin is composed of two alpha and two gamma chains. It is resistant to denaturation by alkali. This forms the basis for its quantitative measurement in the laboratory. This is the predominant Hb in fetal life. It is still present in the newborn and the infant. Beyond first year, only its traces are present. Around 90% Hb beyond 1 year of age is HbF.

Table 32.6: Prevalence of major hemoglobinopathies in the world

Overall	240,000/year
Beta-thalassemia	20%
Beta-thalassemia/HbS	1.6%
HbS	78%

Etiopathogenesis

The basic defect is a hereditary inability to produce beta-chains (normal adult hemoglobin, HbA) which results in erythrocytes that are thin and have short lifespan. The result is hemolytic anemia with characteristic changes in blood and various organs. As a compensatory mechanism, increased production of fetal-hemoglobin (HbF)** occurs.

In the peripheral blood, a large number of normoblasts, target cell and microcytic hypochromic erythrocytes are present. Reticulocyte count is increased. Unless patient has iron deficiency because of some other factor(s), serum iron is normal or high. Bone marrow hyperplasia causes bony changes. Three forms are recognized:

1. **Thalassemia major:** Severe form which is associated with homozygous state.
2. **Thalassemia minor:** Mild form associated with heterozygous state.
3. **Thalassemia trait:** Asymptomatic.

Clinical Features

The disease starts manifesting about 3 months of age with progressive pallor, growth failure, jaundice of varying degree and enlargement of spleen and liver. Recurrent respiratory infections are common. Lymphadenopathy may be present. Physical retardation of growth may be accompanied by hypogonadism.

The facial appearance is characteristic with frontal bossing, prominent maxilla (exposing the teeth), depressed bridge of nose and malocclusion of teeth (Figs 32.9 to 32.11). This appearance is often referred to as **thalassemic** or **hemolytic facies**.

Increased pigmentation of the skin due to high level of melanin in the epithelium and hemosiderin in the dermis may occur. By adolescence, the subject develops significant cardiomyopathy due to chronic anemia and progressive myocardial iron deposition as a result of increased iron turnover. Dysrhythmia, atrioventricular blocks and other conduction disorders, pericarditis and even cardiac tamponade, CCF and electrocardiogram (ECG) repolarization abnormalities may be encountered. Though most cases manifest overt disease after 3–6 months of age (Fig. 32.12), in some it may take 3–5 years.



Fig. 32.9: Thalassemia major. Note the characteristic of hemolytic facies with depressed bridge of nose giving an impression of widely-spaced eyes (pseudohypertelorism), prominent maxilla and malocclusion of teeth, malar prominence severe pallor and mild icterus. Besides growth retardation, the child had moderate splenohepatomegaly.



Fig. 32.10: Thalassemia major. Note the hemolytic facies not as remarkable as in the child in Fig. 32.9 on account of blood transfusion started in second half of first year of life with fair compliance. Spleen size was only grade 2 (just palpable).



Fig. 32.11: Thalassemia major. Note hemolytic facies and growth retardation. She had considerable splenohepatomegaly. Blood transfusion was started in second year of life, but compliance remained poor.

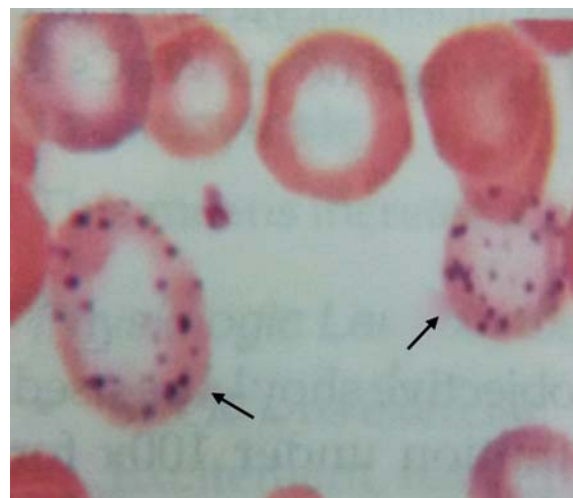


Fig. 32.13: Thalassemia major. Note basophilic stippling which is not seen in IDA. Megaloblastic anemia and lead toxicity may also be accompanied by this finding.



Fig. 32.12: Thalassemia major: Note massive splenomegaly (typically vertically downward as is expected in an infant rather than towards umbilicus seen in older children) with hepatomegaly in a 8-month-old infant with severe anemia (Hb 4.5 g/dL) and failure to thrive.

* It may be low in the presence of another hemoglobinopathy or in case of a recent blood transfusion.

Diagnosis

- **Blood picture** shows a microcytic hypochromic anemia (usually the hemoglobin between 4 and 9 g/dL range), anisocytosis, poikilocytosis, moderate basophilic stippling (Fig. 32.13), nucleated and fragmented erythrocytes, target cells, large number of normoblasts and increased number of reticulocytes (Figs 32.14 and 32.15).
- **Bone marrow** shows erythroid hyperplasia.
- **Osmotic fragility test** reveals a reduced fragility (there is resistance to hemolysis in very dilute, i.e. hypotonic solution).
- **Fetal hemoglobin**, measured by electrophoresis, exceeds 40% of the total*.

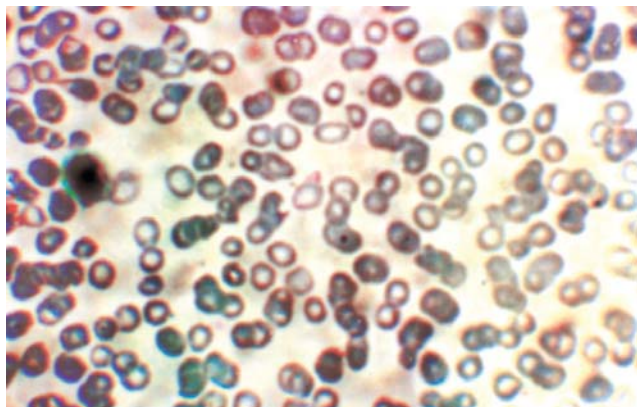


Fig. 32.14: Thalassemia major: Note microcytic hypochromic picture with anisopoikilocytosis. Similar picture may be seen in IDA, anemia of chronic disorders, sideroblastic anemia and lead toxicity.

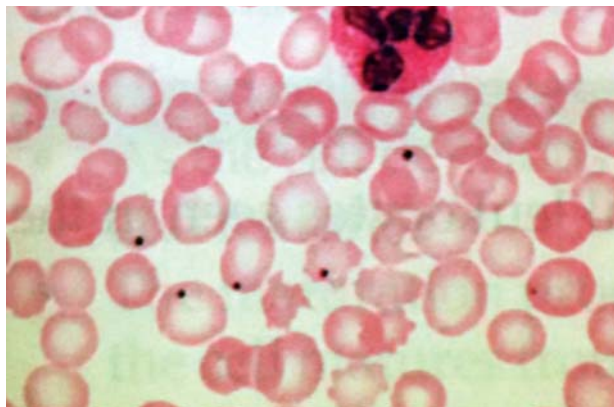


Fig. 32.15: Howell-Jolly bodies. Note that these are small round cytoplasmic RBC inclusion with same staining characteristics as of nucleus. These are seen in hemolytic anemia's, postsplenectomy and megaloblastic anemia.



Fig. 32.16: X-ray hand and forearm showing thinning of the cortex and coarsening of trabeculae in thalassemia major.

- **Radiologic findings** include thinning of the cortex, widening of the medulla (due to marrow hyperplasia) and coarsening of trabeculations in the long bones, metacarpals and metatarsals (Fig. 32.16). Skull shows the hair on end appearance due to vertical striations from widening of the diploic space and atrophy of the outer table of the skull (Fig. 32.17).

Treatment

Bone marrow transplantation (BMT) (more specifically, allogeneic BMT) using a matched sibling donor is currently the only curative treatment for thalassemia. This form of treatment is expensive and not easily available. In the absence of transplant, transfusion-chelation therapy is the only effective treatment available for most of the thalassemics. Blood transfusion is given periodically at 3–5 weeks intervals maintaining hemoglobin at least 9–11 g/dL.

Chelation, since hemosiderosis and hemochromatosis complicating repeated transfusions are per se serious problems, use of an iron chelating agent is recommended (Box 32.5). Iron overload is also from excessive absorption

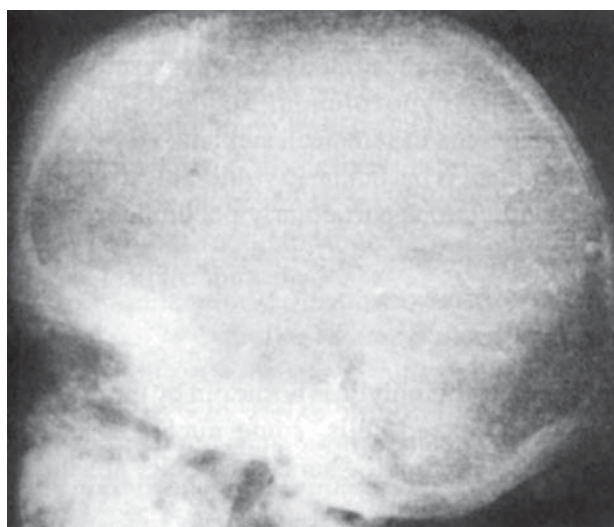


Fig. 32.17: Thalassemia major. X-ray skull showing "hair-on-end" sign. This may be seen in other chronic hemoglobinopathies and chronic IDA as well.

from the gut. Left untreated, it may cause complications such as diabetes mellitus, hypothyroidism, hypoparathyroidism, growth failure and infertility. The best method for measuring iron overload in heart is cardiac T2 magnetic resonance. Alternative methods include serum ferritin, liver biopsy, liver magnetic resonance imaging (MRI) and echocardiography.

Prognosis

The outlook for life in thalassemia major has changed remarkably. Prognosis is clearly related to treatment in the form of high transfusion program and adequacy of chelation therapy. Patients are now surviving into 3rd and 4th decade and beyond and some have married and have children. Cardiac dysfunction occurs even in those receiving adequate desferoxamine (DFO) chelation. For cardiac protection, chelation with deferiprone or combination of both drugs is superior.

Prognosis is clearly related to treatment in the form of high transfusion program and desferoxamine (DFX) therapy. This therapy may also be responsible for hepatitis (prevent-

Box 32.5**Chelation therapy in thalassemia major on regular blood transfusion****Indication**

- 20 blood transfusions
- 1000 serum ferritin level.

Parenteral chelation agent

- Desferrioxamine (Desferal) is the most effective iron chelator available. It is started after 15–20 transfusions and administered subcutaneously with an infusion pump 5–6 times every week.
- Dose is 30–70 mg/kg/day given over 8 hours. Dose needs to be tailored as per body iron overload and urinary excretion of iron. Concurrent administration of vitamin C, 100 mg/day, enhances excretion of iron by chelation. It also facilitates release of iron from ferritin. Maintaining serum ferritin below 1000 ng/mL is the aim. Unfortunately this treatment is expensive.
- High dose intravenous desferrioxamine therapy is indicated in subjects who are poor compliant, have been started on chelation late or have an iron-induced cardiac disease. This is far more expensive than the SC therapy.

Precautions

- Warning about yellow discoloration of urine
- Monitoring ADRs: Periodic ophthalmic and ENT check-up, renal function tests.

Oral chelating agents

- Oral iron chelating agents have been found as an alternative to injectable iron chelating agent.
- The best among the oral agents is *deferiprone* (DFP). It is administered in a dose of 75–100 mg/kg/day in 2–3 divided doses. Its ADRs include joint pains (arthropathy), nausea, vomiting, abdominal pain and agranulocytosis/pancytopenia. Monitoring is important for assessing adequacy of therapy and prevention of serious ADRs.
- Deferasirox, 30 mg/kg/day, claims to be as efficacious as parenteral chelation. ADRs include nausea, vomiting, nephrotoxicity and hepatotoxicity. A careful monitoring is essential.
- Folic acid supplements are recommended, particularly in those receiving suboptimal transfusions therapy.

Vitamin C

- Human recombinant erythropoietin (r-epo) may improve the hemoglobin level in beta-thalassemia intermedia, thereby reducing or obviating the need for blood transfusion therapy.
- Chemotherapeutic agents (5-azacytidine, hydroxyurea* (15–20 mg/kg/day), myleran, butyrate salts) may be employed to stimulate gammaglobulin chain synthesis in thalassemia (as also in sickle cell anemia).
- Prevention of infections is important. Risk of transfusion-related infections (hepatitis B and C and HIV) being there, periodic assessment is warranted. Administration of hepatitis B vaccine must be compulsorily given to these subjects.
- Splenectomy, benefits children who need very frequent blood transfusions or have very big spleen causing discomfort and/or hypersplenism.
- Gene therapy consists of insertion of normal gene within stem cells of recipient. Even incomplete expression of transgene may lessen the severity of the disease significantly.

Abbreviations: ADR, adverse drug reactions; ENT, eyes nose and throat; HIV, human immunodeficiency virus.

* Hydroxyurea is strongly recommended in thalassemia intermedia to cut short the need for blood transfusion. Else, the patient may show growth retardation.

able by hepatitis vaccine), failure of puberty attainment and hypoparathyroidism. Box 32.6 summarizes the various complications resulting from the thalassemia *per se* or its therapy.

Prevention and Counseling

Screening for thalassemia carrier is possible using naked eye single tube red cell osmotic fragility (NESTROF) test or

Box 32.6**Complications of thalassemia major and its treatment**

- Retardation of growth and development.
- **Transfusion transmitted infections:** Hepatitis B, C and D, HIV.
- **Chelation-related problems:** DFX induced low body iron may cause serious neurotoxicity, pancytopenia, cartilage damage and linear growth retardation.
- **Endocrinopathies:** Iron overload, in the absence of chelation therapy, may cause several endocrinopathies, including diabetes mellitus, hypoparathyroidism and hypogonadism.

Abbreviations: HIV, human immunodeficiency virus; DFX, desferrioxamine.

various red cell indices (MCV, RBC count, Mentzer index, RDW etc). Confirmation of carrier status comes from demonstration of elevated HbA₂ on electrophoresis. There are 1 in 4 chances of the disease in the offsprings if both parents are carrier.

Antenatal diagnosis of thalassemia through analysis of fetal blood is now possible by fetoscopy at 18–20 weeks, amniocentesis at 17 weeks or chorionic villous sampling during first trimester, the latter being the procedure of choice currently.

SICKLE CELL ANEMIA

Sickle cell anemia, an autosomal recessive disorder, was, until recently, believed to be confined to the Negro race. However, it is being increasingly detected in some parts of India such as Orissa, Telangana, Madhya Pradesh, Chhattisgarh, Jharkhand and Maharashtra and among Bhanushalis, Budhists and Neo-Budhists.

Etiopathogenesis

Substitution of glutamic acid by valine at 6th position in the beta chain of hemoglobin results in HbS. It is caused by the presence of all the body of hemoglobin in the form of HbS. This hemoglobin forms crescent-shaped crystals under low oxygen tension.

The resultant sickle-shaped erythrocytes (Fig. 32.18) tend to rapidly hemolyze, have a life-span of sheer 10–20 days. Equally importantly, they tend to cause obstruction in the microcirculation, i.e. capillaries (Fig. 32.19), leading tissue hypoxia and infarcts in organs such as spleen, GIT, urinary tract, heart, lungs, brain, bones, tendons and muscles.

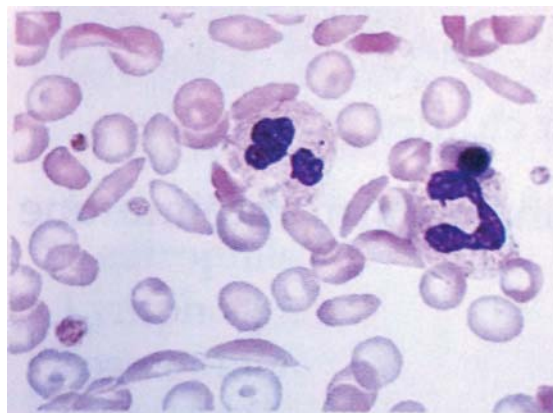


Fig. 32.18: Sickle cell anemia. Note the sickle-shaped RBCs which have tendency to obstruct the microcirculation.

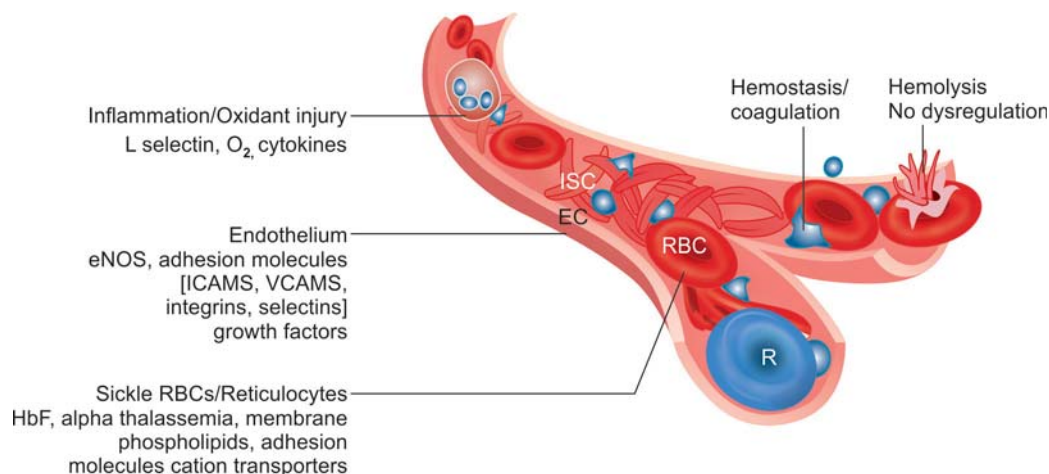


Fig. 32.19: Sickle cell anemia. An artist's modulation of the sickle cells obstructing the microcirculation.

Abbreviations: RBC, red blood cells; HbF, fetal hemoglobin; EC, endothelial cell; ICAM, intracellular adhesion molecule; VCAMS, vascular cell adhesion molecules; ISC, irreversibly sickled cells.



Fig. 32.20: Sickle cell anemia. Note the dactylitis which is a common presenting feature.

Sudden onset of severe hemolysis in sickle cell anemia is called **hemolytic crisis**. Sudden onset of symptoms attributable to vascular occlusion is termed **vaso-occlusive crisis**.

Clinical Features

- Progressive anemia, slight icterus, fever, headache, arthritis and osteopathy of metacarpals and phalanges in particular, i.e. dactylitis (Fig. 32.20).
- Pain is the most frequent and cardinal feature of vaso-occlusive crisis; it is usually precipitated by triggers such as infection and dehydration.
- Spleen is enlarged in the very young but shrinks as also ceases to function (autosplenectomy) in subsequent years following repeated thrombosis*.
- Ulceration of skin overlying the lower limbs.
- Nocturnal enuresis.
- Growth retardation.
- Folic acid deficiency.
- Superadded bacterial infections (*Streptococcus pneumoniae*, *Hemophilus influenzae* type B, *Neisseria meningococcus*, *Salmonella*, *Staphylococcus aureus*, *Escherichia coli*, *Mycoplasma pneumoniae*, *Chlamydia*) and anesthetic complications.
- An enhanced longing for common salt is striking.

- A painful crisis may mimic a surgical abdominal emergency, rheumatic fever or central nervous system (CNS) infection.
 - Poor red cell production together with rapid destruction may lead to aplastic crisis.
- Box 32.7 gives salient features of various crises encountered in sickle cell disease.

Diagnosis

- Evidence of hemolytic anemia is in the form of normochromic red cells, (some nucleated) and reticulocytosis. Sickie-shaped red cells are the most characteristic finding.
- Resistance of red cells to osmotic lysis is increased.
- Electrophoretic pattern shows 50–100% of hemoglobin as HbS and increased amount of HbF.

Treatment

Treatment of HbS disease consists of:

- **Analgesic therapy** for pain crisis, narcotic analgesics may be preferred.
- **Hydration:** It is important to ensure good hydration. Dehydration must be treated with oral rehydration solutions (ORS) and even IV fluids if need be.
- Aggressive treatment of infection.
- **Blood transfusion/exchange blood transfusion:** Blood transfusion therapy is indicated in cases not able to maintain acceptable Hb level (at least 9–11 g/dL), in aplastic. Exchange transfusion may be indicated in cerebrovascular accident, acute chest syndrome and acute sequestration crises and in priapism that persists in spite of rehydration and therapy with analgesics.
- **Folic acid:** Folate therapy should be considered a life-long strategy.
- **Hydroxyurea:** It helps some patients by raising HbF and reducing the frequency and severity of pain crisis, acute chest syndrome and transfusion requirement. Its use should be restricted to more than 5 year-old children.
- Bone marrow transplantation is used with curative intent.

* At a tertiary center in Telangana (MMC, Khammam), it is usual to find splenomegaly even after the age of 5–6 years in established cases of sickle cell anemia. Coexistence of other well-known hemoglobinopathies, which could explain this odd observation, is ruled out. The belt is hyperendemic for malaria.

Box 32.7 Salient features of types of crisis encountered in sickle cell disease

Vaso-occlusive crisis

This is an ischemic injury from obstruction of microcirculation, is characterized by:

- Pain in bones such as femur, tibia and lower vertebrae
- Dactylitis
- Hand or foot syndrome
- Surgical abdomen
- Autosplenectomy by 5–6 years.
- Isothsthenuria—poorly concentrated urine from impaired function of the kidney as a result of papillary necrosis
- Retinal hemorrhages
- Priapism
- Avascular necrosis of femoral head
- Cerebrovascular accident

Acute chest syndrome

- Here microcirculation of lungs is obstructed from veno-occlusion by sickle cells.
- Manifestations include chest pain, cough, wheeze, breathlessness, tachypnea, hypoxemia, fever, etc. Intensive therapy with oxygen, antibiotics, IV fluids, bronchodilators and even steroids is indicated.

Sequestration crisis

Here splenic outflow gets blocked by sickle cells. This causes excessive pooling of blood in spleen which gets considerably engorged. Result is splenic sequestration. Manifestations include hypotension and tachycardia.

Aplastic crisis

- Transient and self-limiting bone marrow failure may occur following a severe infection (usually, parvovirus B19) or folic acid deficiency.
- Severe anemia in this condition may cause CCF.
- No specific treatment is indicated, excepting supportive care and, at times, a transfusion with packed RBCs.

Abbreviations: RBCs, red blood cells; CCF, congestive cardiac failure; IV, intravenous.

Preventive Measures

- **Vaccination:** Pneumococcal, Hib and meningococcal vaccination.
- **Prophylaxis:** Penicillin/amoxicillin prophylaxis which is started in all cases in early infancy and continued at least until 5 years of age.
- **Screening:** Regular screening for development of gallstones.
- **Genetic counseling** for the family.

Prognosis

The younger the patient with severe manifestations, the poorer is the outlook. Intercurrent infections and sickle thrombi in vital organs are the common causes of death.

GLUCOSE 6 PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY

This is an X-linked enzyme deficiency, most common among hereditary enzyme deficiencies with incomplete dominant expression. It occurs mostly in Mediterranean, African, Chinese and Indian stock. Globally, it inflicts over 200 million individuals. Males are predominantly affected. The disease manifests clinically usually following

Box 32.8 Agents known to cause hemolysis in G6PD deficiency subjects

- **Antimalarials:** Primaquine, quinine, mepacrine (quinacrine)
- **Nitrofurans:** Nitrofurantoin, furazolidin, nitrofurazone
- **Sulfas:** Sulfamethoxazole, sulfacetamide, sulfamethoxypyridazine, sulfisoxazole, acetylsulfanilamide
- **Sulfones:** DDS, Sulfoxones, thiazolsulfone
- **Antipyretics/analgesics/anti-inflammatory:** Acetylsalicylic acid (aspirin), NSAIDs (ibuprofen, mefenamic acid), pyridium (phenazopyridine)
- **Antibiotics:** Nalidixic acid, gentamicin, kanamycin, cloxacillin, PAS, novobiocin, chloramphenicol
- **Vitamins:** Vitamin K1 (water-soluble analogues), large doses of vitamin C
- **Miscellaneous:** Quinidine, BAL, methylene blue, probencid, toluidine blue, quinidine naphthalene (moth balls), fava beans (broad beans).

Abbreviations: DDS, diaminodiphenylsulfone; NSAIDs, nonsteroidal anti-inflammatory drugs; PAS, p-aminosalicylic acid; G6PD, glucose 6 phosphate dehydrogenase; BAL, British anti-lewisite.

exposure to certain agents (Box 32.8) and infection(s). Manifestations are related to development of intravascular hemolysis, increased plasma hemoglobin level and hemoglobinuria.

Clinical Features

These vary with the type of deficiency. Three types are usually recognized.

1. **Type 1:** It manifests only on exposure to very powerful oxidant agents such as primaquine, sulfas, vitamin K (heavy doses) and naphthalene. The subject belonging to this type usually escapes developing neonatal hyperbilirubinemia.
2. **Type 2:** The moderate G6PD deficiency in this type manifests on exposure to fava beans, a large number of offending agents and fulminant infection, especially viral hepatitis. In case of viral hepatitis, the individual, icterus becomes not only severe, but also prolonged with enhanced risk of developing hepatic encephalopathy. The hemolysis continues on continuing exposure to offending agent(s). Moreover, neonatal hyperbilirubinemia often occurs in such subjects.
3. **Type 3:** These subjects have a gross G6PD deficiency and develop manifestation (usually anemia) even without exposure to offending factors. A majority of these subjects develop severe neonatal hyperbilirubinemia. Exposure to known offending agents and superadded infection(s) is likely to cause severe hemolysis with hemoglobinuria.

Diagnosis

Screening tests for suspected G6PD deficiency include:

- Demonstration of Heinz bodies (Fig. 32.21) on supravital staining of RBCs
- High plasma hemoglobin
- Raised serum bilirubin (unconjugated)
- Hemoglobin in urine
- Estimation of G6PD enzyme level several weeks after the acute attack of hemolysis is a must for establishing the diagnosis.

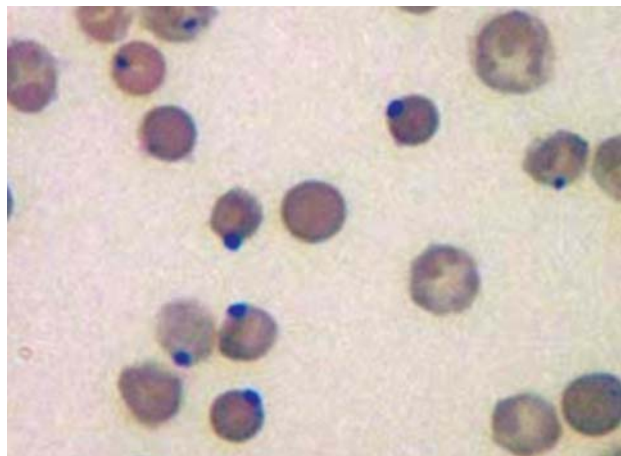


Fig. 32.21: Heinz bodies in G6PD deficiency. These are inclusion of denatured hemoglobin.

Treatment

For severe hemoglobinuria, treatment is administration of sodium bicarbonate for alkalizing urine to safeguard against formation of hematin clots in the renal tubules and renal failure. For severe anemia, blood transfusion is warranted.

Prevention

It consists of avoiding known offending oxidants to known cases of G6PD deficiency and using them with caution in geographical areas or population with high prevalence of this deficiency.

PYRUVATE KINASE DEFICIENCY

This is an autosomal recessive enzymatic defect in which RBCs utilize less glucose than is expected of normal RBCs. As a result, there is lower liberation of adenosine triphosphate (ATP) and leakage of potassium from the cells, leading to lowered life span of RBCs as also their functional defects.

Clinical Features

These include hemolytic anemia and hyperbilirubinemia in neonatal period and varying degree of pallor, icterus and splenomegaly later in life. Besides routine evidence of hemolysis, these patients show autohemolysis that responds to ATP, but not glucose. The diagnosis is established by remarkable reduction in pyruvate kinase level in RBCs.

Treatment

- Severe neonatal hyperbilirubinemia usually warrants an exchange transfusion.
- In later life, treatment consists of giving repeated blood transfusions with supplements of folic acid.
- Splenectomy is indicated in case of severe anemia.

AUTOIMMUNE HEMOLYTIC ANEMIA

In autoimmune hemolytic anemia (AIHA), abnormal antibodies directed against RBCs are produced endogenously by the patient's disordered immune system. Two types are recognized:

1. AIHA associated with warm autoantibodies
2. AIHA associated with cold autoantibodies.

AIHA Associated with Warm Autoantibodies

This may be primary or secondary. In the **primary** or the **idiopathic form**, no underlying cause is found.

In the **secondary** or **symptomatic form**, an underlying disease process like lymphoma, SLE, or immunodeficiency is present. Drugs such as penicillin, cephalosporins, phenacetin, quinidine and methyl dopa that are known to produce AIHA may be considered under this very category. Occasionally, an immune thrombocytopenic purpura may coexist (Evans syndrome). The antibodies involved in this type of AIHA belong to IgG. These antibodies act best at 37°C and hence called **warm**.

Clinical Features

- Manifestations may be acute or chronic.
- In the acute transient type, usually occurring in infants and younger children and preceded by a respiratory tract infection, manifestations include prostration, pallor, jaundice, pyrexia, hemoglobinuria and gross splenomegaly.
- In the chronic form, hemolysis stretches over several months or years.

Laboratory Findings

Laboratory findings include moderate to severe anemia, spherocytosis, polychromasia, fragmented red cells, marked reticulocytosis and a strongly positive direct Coombs test.

Treatment

Treatment in profoundly anemic subjects (least positive Coombs test) is to give compatible blood transfusion(s). In acute transient form, prednisolone, 2.5 mg/kg/day leads to full recovery within 3 months. In chronic form, response to prednisolone is variable and inconsistent. Splenectomy is indicated when anemia continues to be severe after steroid therapy or when very large doses of steroids are needed to maintain a reasonable hemoglobin level. Immunosuppressive therapy, intravenous immunoglobulins, plasmapheresis, etc., deserve to be given a trial before splenectomy in refractory cases.

Prognosis

These children are at more risk for increased morbidity and mortality from more severe and chronic disease. Hemolysis as well as positivity of antiglobulin tests are likely to persist for long time varying from months to years.

AIHA Associated with Cold Autoantibodies

In this AIHA, autoantibodies are more active at low body temperature and belong to IgM class, requiring complement for activity.

Clinical Features

Cold agglutinin disease is characterized by an enormous increase in the cold antibodies following a viral infection or mycoplasmal pneumonia, causing severe episodes of

648 intravascular hemolysis and hemoglobinuria when the patient is exposed to cold. **Paroxysmal cold hemoglobinuria** is remarkable for a specific type of antibody. Designated Donath-Landsteiner hemolysin, it has anti-P specificity. The condition is frequently associated with syphilis.

Treatment

It is in the form of blood transfusions/plasma exchange for severe anemia.

Prognosis

AIHA with cold autoantibodies is an acute self-limiting disease.

METHEMOGLOBINEMIA

This condition is characterized by chocolate-colored blood that fails to turn red even on aeration because of HbM.

It may exist as an autosomal dominant inherited disorder of hemoglobin M when the subject is cyanosed since birth or as an inherited disorder of RBC enzymes, methemoglobin reductase deficiency. In the latter situation, methemoglobinemia follows exposure to strong oxidants like analgesics, anesthetics, aniline dyes, antimalarials, nitrites, sulfas, vitamin K analogue and naphthalene.

- **Diagnosis** is confirmed by spectrophotometry of hemoglobin electrophoresis at pH 7.
- **Prevention** is by avoiding exposure to known offending agents.
- **Treatment** is in the form of methylene blue (IV followed by oral) or vitamin C over a prolonged period.

APLASTIC ANEMIA

(Bone Marrow Failure Syndrome, Pancytopenia)

Aplastic anemia, a group of hematopoietic stem cell disorders causing suppression of erythroid, myeloid and megakaryocytic cell lines, is no longer considered a doom. With modern treatment, prognosis has considerably improved. In India, its incidence is believed to be higher than incidence of 2–6 individuals per 1,000,000 population in the west.

Definition

Aplastic anemia is defined as a bone marrow failure causing involvement of all the blood elements Pancytopenia and hypocellular marrow (Fig. 32.22) are its crux. Involvement of only red cells is called the **hypoplastic anemia**, of granulocytes the **agranulocytosis** and of platelets the **thrombocytopenia**.

Etiopathogenesis

The fundamental cause is absence of the hematopoietic stem cell as a result of:

- Infection(s)—usually viruses
- Toxins/chemicals
- Immunological suppression of bone marrow—oncological conditions
- Unfavorable microenvironment in bone marrow

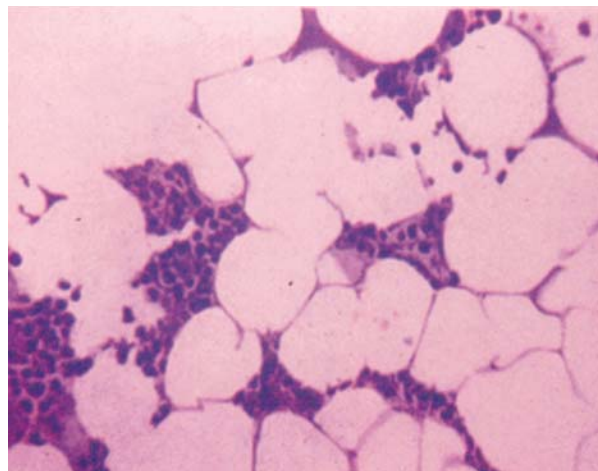


Fig. 32.22: Aplastic anemia. Note the classical hypocellular marrow. The bone marrow is occupied largely by the stromal and fatty tissue instead of hematopoietic cells.

- Mutations in genes that control hematopoiesis Fanconi anemia, Blackfan-Diamond syndrome, dyskeratosis congenital, amegakaryocytic thrombocytopenia and thrombocytopenic absent radii.

Clinical Features/Types

- Congenital (constitutional) aplastic anemia may be:
 - **Fanconi anemia:** Autosomal recessive; multiple congenital anomalies such as microcephaly, mental retardation, microphthalmia, squint, nystagmus, short stature, hypogonadism, defects of thumb (absence) and radius (absence), brown pigmentation of the skin, café-au-lait spots, dextrocardia and renal anomalies. Diagnosis is confirmed by induced chromosomal breakage test (diepoxybutane/mitomycin C test). While 90% develop aplastic anemia, 10% present with other malignancies including acute myeloid leukemia (AML), myelodysplasia or liver cancer.
 - **Dyskeratosis congenital:** X-linked recessive; reticular skin pigmentation, mucosal leukoplakia, nail dystrophy, vulnerability to fractures.
 - **Amegakaryocytic thrombocytopenia:** Autosomal recessive. No associated anomalies.
 - **Blackfan-Diamond syndrome (constitutional pure red cell anemia):** Autosomal dominant, autosomal recessive; short stature, congenital defects, macrocytosis, high fetal Hb and high adenosine deaminase.
 - Shwachman-Diamond syndrome—Exocrine pancreatic insufficiency.
 - Thrombocytopenia absent radii (TAR) syndrome.
- **Acquired aplastic anemia:** It may result from:
 - Viral, bacterial or parasitic infections (HIV, HB, Epstein-Barr Virus {EBV}).
 - Infiltration of marrow by malignant tissue as in leukemia, Niemann-Pick and Gaucher diseases.
 - Osteopetrosis (marble bone disease).
 - Irradiation from chemicals and drugs such as chloramphenicol, antimetabolites, phenylbutazone, etc.
 - Immune mediated stem cell loss.

Management consists of stopping exposure to the possible cause, giving frequent blood transfusions and administering androgenic anabolic steroids as such or together with corticosteroids. Antibiotic cover is recommended.

Investigations

Though CBC gives fairly good idea of bone marrow failure, it is mandatory to do bone marrow aspiration and biopsy for confirmation of diagnosis.

Treatment

From the management point of view, acquired aplastic anemia is graded according to severity. Presence of two of the following peripheral blood criteria puts the disease in category of severe aplastic anemia (SSA).

- Corrected reticulocyte count less than one per cent
- Absolute neutrophil count less than $500/\text{mm}^3$
- Platelet count less than $20,000/\text{mm}^3$ and presence of hypoplastic or aplastic bone marrow

Cases with absolute neutrophil count less than $200/\text{mm}^5$ are labeled as having very severe aplastic anemia (VSAA): This classification is useful for prognosis also. For SAA and VSAA the treatment of choice is allogeneic BMT, more precisely hematopoietic stem cell transplantation (HSCT)*.

In the absence of BMT, intensive immunotherapy is used with anti-lymphocyte or anti-thymocyte globulin, cyclosporine with or without prednisolone. Monotherapy with cyclosporine or methylprednisolone are other options. Fanconi's anemia responds to androgen therapy.

Till the time patients respond to therapy, control of anemia and bleeding is required with transfusions of packed RBC or platelets. Infections need to be treated with appropriate antibiotics.

MECHANISM OF COAGULATION (Hemostasis)

Hemostasis involves local reactions of blood vessels, multiple activities of the platelets, interaction of coagulation factors, inhibitors and fibrinolytic proteins circulating in the blood. It plays a vital role in maintaining a dynamic equilibrium between fluidity and coagulation so that neither excessive bleeding nor thrombosis occurs spontaneously or after a minor trauma.

Hemostatic mechanism may be primary or secondary. The former relates to vascular response and platelet plug formation, and the latter to the formation of a stable fibrin clot (Fig. 32.23).

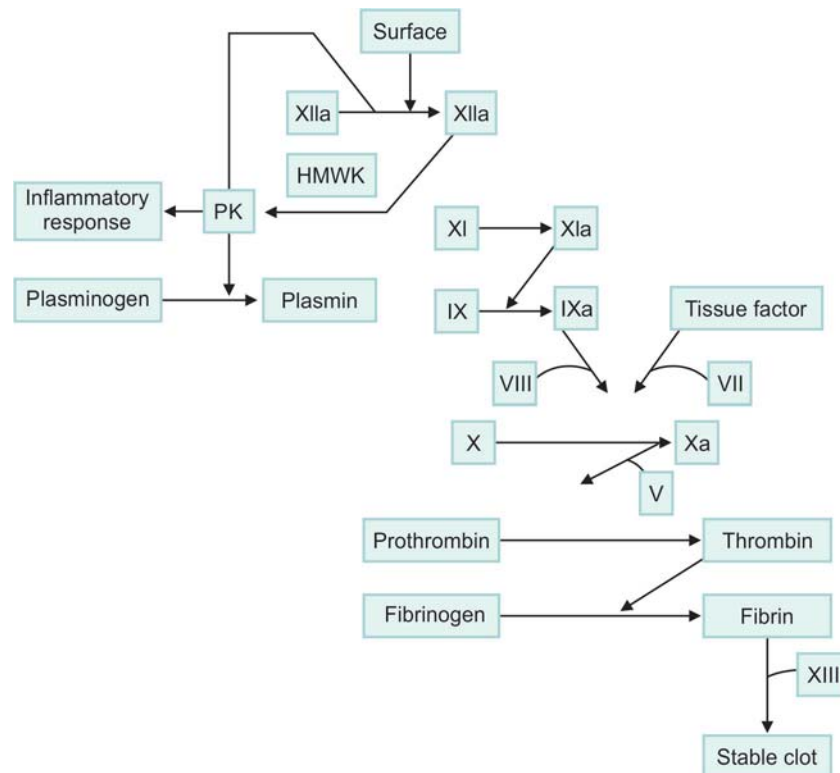


Fig. 32.23: Coagulation. Schematic representation of its mechanism.

Note: Factors	I Fibrinogen	II Prothrombin	XII Hageman factor	XIIa Activated form
	V Labile factor	VII Antihemophilic (AHF)	XIII Fibrin stabilizing factor, fibrinase	
	IX Plasma thromboplastin component	IXa Activated form	PK Prekallikrein (Fletcher factor)	HMWK High-molecular weight kininogen
	X Stuart-prower (SO) factor			
	XI Plasma thromboplastin antecedent (PTA)	XIa Activated form		

* HSCT may be autologous (stem cells harvested from patient per se) or allogeneic (stem cells from a donor). The site of stem cells is usually cord blood or peripheral blood.

Box 32.9 Classification of coagulation disorders**Congenital disorder**

- **Phase I disorders:** Factor VIII deficiency (classical hemophilia, hemophilia A), Factor IX deficiency (Christmas disease hemophilia B), Factor XI deficiency (hemophilia C), Factor XII deficiency (Hageman factor deficiency), Von Willebrand disease (vascular hemophilia)
- **Phase II disorders:** Deficiency of a factor in prothrombin complex (factors II, V, VII and X)
- **Phase III disorders:** Congenital afibrinogenemia, congenital dysfibrinogenemia
- Factor XII deficiency (fibrin-stabilizing factor deficiency)

Acquired disorder

- Vitamin K deficiency hemorrhagic disease of the newborn
- Postneonatal vitamin K deficiency (late hemorrhagic disease)
- Liver disease
- Deficiency of all factors except factor VIII, DIC, hyperfibrinolysis inhibitors
- Circulating anticoagulants in SLE, lymphoma, penicillin or other drug reactions. DIC Septic shock, etc.

Abbreviations: SLE, systemic lupus erythematosus; DIC, disseminated intravascular coagulation.

Coagulation has three phases. In **phase I**, there is formation of thromboplastic by the interaction of certain coagulation factors, phospholipids and tissue juice containing tissue factor. **Phase II** involves conversion of prothrombin (factor II) to thrombin (factor II a). In **phase III**, thrombin converts soluble fibrinogen to fibrin. Disordered coagulation causes a number of disorders (Box 32.9).

APPROACH TO A CHILD WITH BLEEDING/HEMOSTATIC DISORDER

History and Physical Examination

The enquiry must aim at determining if the defect is congenital (inherited) or acquired and basically a coagulation or a bleeding disorder. Attempt to determine the site(s) of bleeding, its severity, its duration, and the age of onset, whether spontaneous or precipitated by some factor, the experience with prior surgical procedure and trauma, family history, drug history and, in girls, the menstrual history.

Physical examination should determine whether the bleeding is petechiae, ecchymosis, hematomas, hemarthrosis or mucosa bleeding. The evidence of a primary systemic disease must be sought. After the thorough history and physical examination, some provisional impression should be formed based on the clues thus provided. For instance:

- Development of petechiae or ecchymosis spontaneously (without a precipitating factor such as trauma) points to a bleeding disorder (purpura).
- Bleeding from umbilicus, if prolonged and occurring in a neonate, points to congenital type of plasma clotting factor disorders. Purpura, as a rule, manifests later in life.
- Availability of a positive family history of bleeding disorder usually points to existence of a plasma coagulation disorder.
- Deep bleeding into joints and muscles, diffuse spreading ecchymosis and hematomas suggest disorder of coagulation system.

- Mucosal bleeding (epistaxis, hematuria, menorrhagia, GIT bleed), petechiae in skin and mucous membrane and ecchymotic lesions that are small and multiple points to purpura.

Investigations

Initial investigations should include prothrombin time, partial thromboplastin time and platelet count.

- **CBC**, including total leukocyte count (TLC), to exclude sepsis.
- **Blood smear** to exclude DIC.
- **Prothrombin time (PT)**, the time taken for plasma to clot following addition of exogenous thromboplastin (tissue factor) and calcium, varies from 11.5–14 seconds. A prolonged PT suggests a deficiency of factors II, V, VII and/or X.
- **Activated partial thromboplastin time (APTT)**, time needed for clotting of plasma (that has been activated by incubation with an inert activator such as ground glass ellagic acid or kaolin) on addition of calcium of platelets, varies from 25–40 seconds. This test evaluates the adequacy of factors VIII, IX, XI and XII.
- In case both PT and PTT are prolonged, one should consider vitamin K deficiency, advanced liver disease and congenital deficiency of factors V and X.
- **Platelet count** is essential in the evaluation of a child with bleeding disorder. A count of less than 20,000/mm³ causes considerable bleeding. Thrombocytopenia is the most common cause of a primary hemostatic defect with overt bleeding.
- **Bleeding time (BT)** is considered to be the best test for evaluating the vascular and the platelet phases of hemostasis. Nonetheless, in view of issues concerning its reproducibility and reliability, it has lost its shine. Instead, platelet aggregation studies are being increasingly employed for platelet function disorders. Normal bleeding time varies between 1–3 minute and clotting time 3–10 minutes. Table 32.7 lists the situations in which clotting time (CT) and bleeding time are prolonged.

Table 32.7: Situations in which clotting time and bleeding time are prolonged

CT/BT	Disorder
Prolonged CT	
With high PT	Factor VII deficiency
With high APTT	Factor VIII, IX, XI and XII deficiency, Von Will brand's disease
With high PT and APTT	Vitamin K deficiency, advanced liver disease, DIC, factors V, X, fibrinogen deficiency.
Prolonged BT	
With low platelet count	ITP, drug-induced purpura, leukemia or bone marrow.
With normal platelet count	Henoch-Schoenlein purpura

Abbreviations: BT, bleeding time; CT, clotting time; PT, prothrombin time; APTT, activated partial thromboplastin time; ITP, immune thrombocytopenic purpura; DIC, disseminated intravascular coagulation.

There is an inverse relationship between the BT and the platelet count. In other words, lower the platelet count, more prolonged the BT is likely to be. A high BT with reduced platelet count suggests idiopathic thrombocytopenic purpura or purpura secondary to bone marrow aplasia or leukemia. A high BT in the presence of normal platelet count points to anaphylactoid purpura or platelet dysfunction.

Mixing study consists of adding normal plasma to the plasma of the patient. If the PTT on the mixture is normal, it means that the patient's abnormal PTT stands corrected and the deficiency state is present. This point to a deficiency of VIII, IX, or XI. If the study fails to correct the defect, an inhibitor against factors VIII, IX or XI must be suspected.

Thrombin time, the time needed for plasma to clot after the addition of bovine or human thrombin (factor IIa), varies from 15–20 seconds. It is prolonged in hypofibrinogenemia, dysfibrinogenemia and heparin contamination. **D-Dimer assays** is now considered superior to fibrin split products (FSP) assays for measuring degradation products of fibrin found in the plasma in DIC and liver disease. Levels (normal <0.5 mg/mL) are also raised in DIC, deep vein thrombosis and pulmonary embolism. **Apt test** is employed to exclude maternal blood in a bleeding neonate.

Other tests include euglobulin clot lysis time (ECLT), assays for plasminogen, plasminogen activators and inhibitors and immunologic assays for fibrin split products. According to current recommendations, the previously used tests such as tourniquet test, prothrombin consumption time and thromboplastin generation test lack specificity and sensitivity or happen to be cumbersome and difficult to interpret.

DISSEMINATED INTRAVASCULAR COAGULATION

(Disseminated Intravascular Coagulopathy, Consumptive Coagulopathy)

Definition

Disseminated intravascular coagulopathy syndrome is characterized by consumption of certain coagulation fac-

tors (usually factors II, V and VIII), leading to widespread intravascular deposition of fibrin, bleeding from multiple sites and hemolytic anemia.

Etiopathogenesis

Several pathologic processes, including hypoxia, acidosis, tissue necrosis, endothelial damage and shock, trigger DIC (Fig. 32.24). Understandably, a large number of diseases may be accompanied by DIC (Table 32.8). Nevertheless, Gram-negative septicemia is the most common followed by Gram-positive septicemia.

The process involved in development of DIC is depicted in Figure 32.25. One or more factors such as hypoxia, acidosis, tissue necrosis, shock and endothelial damage trigger intravascular activation of the clotting factors. The intravascular coagulation is followed by consumption of coagulation factors, leading to reduction in levels of factor I (fibrinogen), factor VII and platelet count. The formation of fibrin causes vascular occlusion and blockade of reticuloendothelial system. The activators released from damaged endothelium, platelets and leukocytes activate plasminogen. The latter is also activated directly by factor XII and thrombin.

The enhanced fibrinolytic activity leads to production and accumulation of massive fibrinogen degradation products (FDP) which result in platelet dysfunction. This prevents transformation of fibrinogen to fibrin, thereby further worsening bleeding. Remember, the neonate is more vulnerable to develop acute DIC.

Clinical Features

In addition to the manifestations of the causative condition/disease *per se*, the hallmark of clinical picture is constituted by a generalized bleeding diathesis. To begin with, bleeding occurs from sites of venipuncture or surgical incision. This is followed by widespread ecchymosis, petechiae, epistaxis, subconjunctival hemorrhages, hematuria, etc.

Microvascular thrombi may cause infarction of massive areas of skin, subcutaneous tissue and many organs. End-

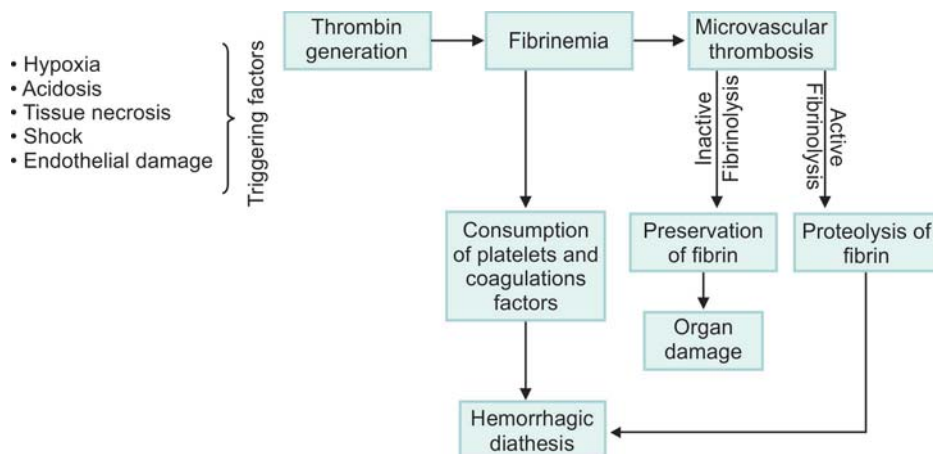


Fig. 32.24: Etiopathogenesis of DIC. Note that, besides consumption of coagulation factors, including platelets, proteolysis of fibrin preceded by active fibrinolysis of microvascular thrombosis play considerable role in this phenomenon, leading to hemorrhagic diathesis.

Table 32.8: Etiology of disseminated intravascular coagulation syndrome

Acute DIC	Chronic DIC	Neonatal DIC
Infections <ul style="list-style-type: none"> Bacterial <ul style="list-style-type: none"> Gram-negative septicemia Gram-positive septicemia Viral Rickettsial Fungal Protozoal <ul style="list-style-type: none"> <i>P. falciparum</i> malaria 	Malignancies <ul style="list-style-type: none"> Monocytic leukemias Disseminated neuroblastoma Cardiovascular disorders <ul style="list-style-type: none"> Shock Cyanotic congenital heart diseases Giant hemangiomas Hemolytic anemias <ul style="list-style-type: none"> Thalassemia major Sickle-cell anemia 	<ul style="list-style-type: none"> Asphyxia Hypothermia Shock
Trauma <ul style="list-style-type: none"> Crush injury Burns Major surgery 	Collagen vascular disease <ul style="list-style-type: none"> SLE HSP Polyarteritis nodosa 	
Miscellaneous <ul style="list-style-type: none"> Snake bite Acute hepatic failure Hemolytic-uremic syndrome Mismatched blood transfusion Acute promyelocytic leukemia 		

Abbreviations: DIC, disseminated intravascular coagulation; SLE, systemic lupus erythematosus; HSP, Henoch Schoenlein purpura.



Fig. 32.25: Disseminated intravascular coagulation. Note bleeding from multiple sites—petechiae, bleeding from nostrils and hematuria. Even venipuncture sites showed bleeding. The critically sick neonate with sepsis had hepatosplenomegaly as well.

organ damage may result in intracranial bleed, pulmonary edema and acute respiratory distress syndrome, acute renal failure, peripheral cyanosis and even gangrene. Shock and severe metabolic derangements may well be secondary to DIC as also the primary disease *per se*. Purpura fulminans may occur because of wide-spread thrombotic occlusion of dermal vessels, leading to sharply demarcated large patches of ecchymoses that may worsen to develop skin infarction.

Profound anemia as a result of hemolysis develops rapidly. In case of chronic DIC, symptoms of primary disease rather than those because of DIC dominate the scenario. Prominent DIC symptoms are subtle and include intermittent skin or mucosal bleeds developing over weeks or months, thrombophlebitis at unusual sites, and deep venous thromboembolism.

Diagnosis

The blood smear shows fragmented burr and helmet-shaped red cells, the so-called **schizocytes**, as a result of microangiopathy. In addition, platelets are reduced, fibrinogen level is low, prothrombin time, partial thromboplastin time and thrombin time are low, fibrin split products are present in blood, and factor VIII level is low. Supportive tests include D-dimers which is quite characteristic.

Treatment

Management of the underlying disease such as sepsis, snake bite, burns, etc is a must. Early recognition and control of the DIC syndrome and management of the triggering factors (shock, hypoxia, dyselectrolytemia) form the sheet-anchor of successful treatment. An IV line should be set up to avoid repeated venipuncture.

Replacement therapy is in the form of fresh blood transfusion (preferably platelet infusion for thrombocytopenia, cryoprecipitates for hypofibrinogenemia, fresh or frozen plasma for replacement of other coagulation factors and natural inhibitors) is of definite value. Exchange transfusion (double volume) assists by eliminating toxins, circulating fibrin split products and activated procoagulants and by supplying the replacement factors.

Specific **anticoagulant therapy** is indicated when replacement therapy proves ineffective in controlling the bleeding, or treatment of primary disease is inadequate or incomplete. The drug of choice, heparin, 1 mg (100 units)/kg, may be given as bolus followed by continuous infusion of 15–25 units/kg/hour. Administration of heparin must be monitored by serial measurements of platelet count and plasma fibrinogen concentration. Remaining supportive measures include vitamin K for correcting vitamin K dependent factors and steroids (hydrocortisone) in special situations such as meningococcemia and purpura fulminans.

Prognosis

Notwithstanding best of treatment, acute DIC has a poor prognosis with a mortality of 50–80%, the highest mortality being in neonates.

VITAMIN K DEFICIENCY BLEEDING (Hemorrhagic Disease of the Newborn)

Vitamin K deficiency bleeding (VKDB), earlier termed **hemorrhagic disease of the newborn**, is defined as a “bleeding due to inadequate activities of VK dependent coagulation factors (II, VII, IX, X), which is correctable by vitamin K replacement.”

On the basis of age of onset VKDB is classified as early (onset <24 hours), **classical** (onset first week of life excluding first 24 hours) and **late** (beginning day 8 of life or later). Most cases of late VKDB (L-VKDB) are seen up to 12 weeks of age, but to include more such cases the upper age limit stands extended to six months. For more details, refer Chapter.

HEMOPHILIA

It is the most common of the hereditary bleeding disorders, constituting nearly 90–95% of such cases.

Classification

- **Hemophilia A (classical hemophilia):** It results from deficiency of factor VIII, the antihemophilic factor (AHF). It is X-linked recessive, occurring almost exclusively in the males*. The females act as the carriers without manifesting the disease. Hemophilia A accounts for 98% of all the hemophilics. The incidence in the population is 1 in 10 thousands.
- **Hemophilia B (christmas disease):** It results from deficiency of factor IX, the plasma thromboplastin component (PTC).
- **Hemophilia C:** It results from deficiency of factor XI, the plasma thromboplastin antecedent (PTA).

Clinical Features

- Manifestations depend on the extent of deficiency of the clotting factor. About one-third hemophilics have just mild disease. They are called **subhemophilics**.
- Earliest manifestation may be in the form of bleeding from the umbilical cord within few days after birth or excessive bleeding following circumcision.
- Later, tendency to have excessive bleeding, contusions or hematomas at sites of minor trauma, epistaxis, and bleeding after tooth extraction or tonsillectomy are the common presenting features.
- Hemarthrosis, especially of knee, ankle and elbow, is a characteristic feature. The joint becomes swollen and painful. In the earlier stages, the hemorrhage within the joint gets absorbed. Repeated attacks may cause inflammation and degenerative changes, the joint ultimately becoming immobile, the so-called **fixed joint** (Fig. 32.26).
- Bleeding may occur into genitourinary tract, CNS, GIT, liver, spleen, peritoneal or pleural cavity—in fact anywhere. Skin is not spared but, unlike in purpura, petechiae do not occur in hemophilia.

Diagnosis

Clinical Evaluation

Clinical picture and family history of the disease on maternal side, especially maternal uncles are highly suggestive. Hemophilia is, however, sporadic in 30% of instances and it may not be traceable in the pedigree.

* Rarely, a female may suffer when an affected male marries a female carrier.

** Even BT may be prolonged in some 20% cases of hemophilia.



Fig. 32.26: Hemophilic knee hemarthrosis. Note the muscle atrophy and nearly fixed unstable joints from degenerative changes following repeated hemorrhages (hemarthrosis) in a child suffering from classical hemophilia. With each fresh bleed, the joint becomes inflamed and painful.

Investigative Evaluation

- **Blood tests:** Clotting time is prolonged, bleeding and prothrombin times are normal**. Clot retraction is also normal. Prothrombin consumption is low. Thromboplastin generation is high. The confirmation of the diagnosis is by specific factor assay.
- **Radiology:** It should be done in cases of hemarthrosis. Initially, there is distention of the joint cavity and synovitis. Later, the changes include areas of synovial thickening, demineralization, erosion and contraction. Increased vascularization of joint space results in accelerated bone growth. Thus, premature appearance of ossification centers may occur. Also, there may be complete destruction of articular surface and formation of juxta-articular cysts.

Antenatal Diagnosis

It is possible at 18–20 weeks of gestation by:

- Procuring fetal blood and demonstrating low level of pre-coagulant component of factor VIII employing DNA probe to amniotic fluid fibroblast
- Employing molecular biology technique on chorionic villus sampling
- Polymerase chain reaction (PCR) technique or oligonucleotide primers

Carrier detection is possible by determining that the factor VIII C and F VIII Ag ratio is <0.6 (normal 1) or by identifying mutation on DNA studies.

Treatment

Specific measures: These consist of giving replacement therapy for the missing clotting factor. In case there is severe bleeding, fresh whole blood and, in case of mild to moderate bleeding, fresh frozen plasma are recommended. Factor VIII concentrates, especially recombinant ones, are now preferred over cryoprecipitate as the source of coagulation factors because of their safety. These are dispensed lyophilized powder in containers of 250 or 500 units and need easy reconstitution before actual use.

Dose of factor VIII (units) = Desired rise (unit/dL, percent) × body weight (kg) × 1.3 – 1.5.

This should be given 12 hourly. These are expensive and not freely available in India and other developing countries. Hence, the practical choice in a vast majority of the cases remains cryoprecipitate. It is workable to prepare it in any reasonable blood bank from fresh plasma. A 250 mL of fresh plasma yields one bag of cryoprecipitate that contains 75–125 units of factor VIII. A single bag of cryoprecipitate per 5 kg body weight raises the patient's factor VIII level to 50% of normal. In minor bleeding episodes like mucosal bleeding (epistaxis, small hematomas, mouth bleed and dental extractions, recommended drugs are:

- Desmopressin and danazol which raise the factor VIII and perhaps factor IX levels 25–50% above baseline.
- Antifibrinolytic agents (tranexamic acid, epsilon aminocaproic acid) for 5–10 days.

In western countries, home treatment that provides for storage of factor VIII concentrates at home and their reconstitution and IV infusion right at home is now becoming popular.

Symptomatic measures: Local treatment of wounds consists of:

- Cleansing the open injury
- Rest
- Ice—local cold to achieve vasoconstriction RICE
- Compression—pressure bandage
- Elevation of the part
- Local application of thrombin powder or foam.

For hemarthrosis, the initial treatment is rest and immobilization of the joint and application of ice bags/packs. Later, local heat and physiotherapy to prevent ankylosis should be given. For pain, use of analgesics is of advantage. Some authorities favor the use of steroids in cases of hemarthrosis. Don't include IM injections, contact sports and nonsteroidal anti-inflammatory drugs (NSAIDs) (including aspirin).

Preventive Care

- Prevention of trauma must begin right from crib (which needs to be padded).
- Regular exercise for strengthening muscles, protecting joints and improving fitness.
- Drugs adversely affecting platelet function, like aspirin and NSAIDs, should be avoided.
- Avoiding contact sports.
- Maintaining a healthy body weight to avoid extra stress and strain on joints.
- Hepatitis B vaccine must be given as early as possible by SC route. A hemophiliac is likely to be exposed to the risk of blood products throughout life.
- Since there is as yet no vaccine against acquired immunodeficiency syndrome (AIDS), a very careful testing of the blood product for HIV before transfusion is the only precautionary measure available with us.
- Genetic counseling should include guidance for pre-natal diagnosis.

Prognosis

The hemophilic patient is always in danger of severe bleeding. Some die in infancy and early childhood. Recurrent hemarthrosis may produce crippling. If trauma and infection can be prevented, activity reduced and adequate treatment administered, outlook for life is good. Unfortunately, repeated transfusions may produce anticoagulation factor, thus adding to the difficulties in management.

VON WILLEBRAND DISEASE (VWD)

This autosomal dominant disorder is characterized by disproportionate bleeding following minor trauma as observed in hemophilia. However, clotting time is normal and bleeding time is prolonged. The cause appears to be the deficiency of the so-called **Von Willebrand factor** (VWF), resulting in reduced synthesis of factor VIII and diminished platelet adhesiveness.

Diagnosis is by demonstrating prolonged bleeding time and reduced factor VIII. A noteworthy point is that whereas ristocetin-induced aggregation is normal in classic hemophilia, it is reduced in VWD. In order to check bleeding, an infusion of fresh or fresh frozen plasma is usually enough. For serious bleeding, cryoprecipitate therapy is preferred.

IMMUNE THROMBOCYTOPENIC PURPURA

(Idiopathic Thrombocytopenic Purpura, Werlhof's Disease, Purpura Hemorrhagic)

Idiopathic thrombocytopenic purpura (ITP) is the most common bleeding disorder of childhood. ITP is of special interest in pediatric practice. It is estimated that three-fourth of all cases of this disease are children. Secondly, it has the following distinctive features that are not seen in adults:

- Both sexes seem to be equally affected in children whereas adult form is known to have a predilection for the females.
- About 85–90% children with ITP may have spontaneous remission. In adults, remission occurs in just one-third of cases.
- Unlike in adults, antiplatelet-autoagglutinins have been infrequently demonstrated in children suffering from this disorder.

Definition

ITP is defined as occurrence of spontaneous small hemorrhages in the skin, mucous membrane and internal organs as a result of thrombocytopenia from autoantibody-mediated consumption of platelets. There are increased bleeding time, gross deficiency in the number of circulating platelets and normal or increased megakaryocytes in the bone marrow.

Etiopathogenesis

Etiology is not entirely clear. There is a widespread feeling that ITP, like acquired autoimmune hemolytic ane-

mia, may well be one of the autoimmune diseases. The evidence is, however, equivocal. As already mentioned, autoagglutinins are only infrequently demonstrated in the childhood form, a point most often cited against this hypothesis. Here it is worth remembering that there are many other serum factors that, though present in certain diseases of adults, are absent in the childhood counterparts. For instance, in glandular fever (infectious mononucleosis), the heterophil agglutinin test is very frequently negative in children whereas it is often positive in adults. Serology in rheumatoid arthritis is positive in 80% of adult patients, but very rarely so in children.

In a large proportion of the cases of ITP, a mild viral upper respiratory infection precedes by 1–4 weeks. In view of the high frequency of such infections in childhood, this observation cannot be considered to be causally related. The possible role of spleen remains to be established. The basic pathology that causes bleeding in ITP is two-fold—increased vascular permeability and thrombocytopenia.

Clinical Features

The usual age of onset is 1–8 years, the median being 5 years. Two forms of the disease are known—acute and chronic.

Acute Type

This is the type generally seen in childhood. In about one-half of the cases, it is preceded by an infection, especially of the upper respiratory tract, 1–4 weeks earlier. Onset of ITP is sudden and the child presents with bruising, petechiae and bleeding from the mucosal surface, e.g. nose, gums, eyes and urinary tract (Figs 32.27A to C, to 32.29). Spleen may be just palpable in 25% of the cases.

After a few days, there is reduction in bleeding due to an improvement in capillary integrity though thrombocytopenia is still present. Death may occur in the acute phase from uncontrolled bleeding or intracranial hemorrhage (ICH). ICH is, however, infrequent (1 in 1000). Its risk is greatest at platelet count under $10,000/\text{mm}^3$. The patient may completely recover in 6 months. A small percentage of cases pass on to the chronic stage.

Chronic Type

When ITP exists for more than 6 months despite steroid therapy, it is termed **chronic**. This form accounts for about 10–15% cases of childhood ITP. There is usually a prolonged history of bleeding or a bruising tendency. The course is marked by relapses and remissions. The bleeding



Figs 32.27A to C: Immune thrombocytopenic purpura: (A) and (B) Petechiae and purpura; (C) Echymosis.



Fig. 32.28: Immune thrombocytopenic purpura. Note the subconjunctival hemorrhage. Despite bruising and petechial rash, and epistaxis, the child appeared fairly well. Platelet count was $18,000/\text{mm}^3$.



Fig. 32.29: Immune thrombocytopenic purpura. Note the extensive buccal mucosal and gum bleed.

656 is usually less severe due to less severe involvement of the capillaries. Chronic cases seldom die from this condition which may persist for years together.

Diagnosis

When a child presents with purpura, a careful history should be obtained with special reference to a preceding infection, recent drug therapy and possible exposure to irradiation and chemical agents such as toxins, sprays and insecticides. Various tests should include:

- Tourniquet/Hess test* is positive.
- Complete hemogram to find out hemoglobin status and any abnormal cells
- Platelet count is usually less than 20 thousands/mm³ (Fig. 32.30).
- Bleeding, clotting and clot retraction times are abnormal since they depend on platelet function.
- Bone marrow to ascertain the adequacy of megakaryocytes and to rule out leukemia and aplastic anemia.
- In ITP, normal or increased numbers of megakaryocytes (Fig. 32.31) are seen. Some megakaryocytes are immature with deep basophilic cytoplasm. Scanty platelet budding may be present. Modest eosinophilia is usual.
- Culture from the nasopharynx, antibody titers and an lupus erythematosus (LE) cell preparation.

Differential Diagnosis

- ITP must be differentiated from purpura secondary to aplastic anemia, leukemia and other infiltrative processes of the bone marrow.
- In infants, it needs to be distinguished from genetically determined thrombocytopenia's.
- In older children, such conditions as SLE, lymphomas and AIDS (when they manifest with thrombocytopenic purpura) must be considered.
- When thrombocytopenic purpura is accompanied by significant splenomegaly, congestive splenomegaly secondary to primary liver disease, lipidosis and reticuloendotheliosis must be excluded.

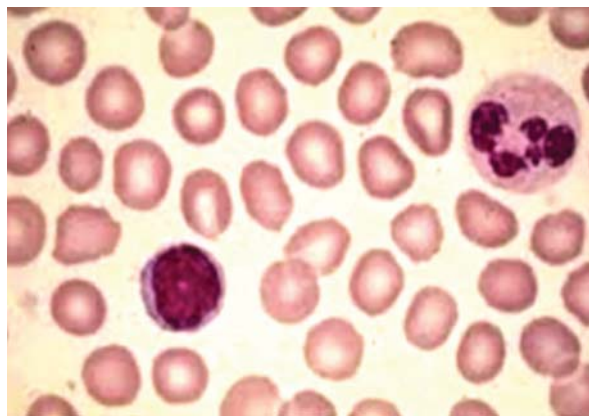


Fig. 32.30: Immune thrombocytopenic purpura. Note remarkable reduction in platelets in the peripheral blood film.

* **Hess test:** On the flexor aspect of the forearm, mark an area 2.5 cm². Notice if any purpuric spots are present. Now apply the blood pressure cuff. Record systolic and diastolic pressures. Maintain the pressure between the two readings for 5 minutes. After the cuff is deflated appearance of more than 8 fresh spots in the circumscribed area indicates a positive test. In case numerous petechiae appear before the deadline of 5 minutes, deflate the cuff immediately.

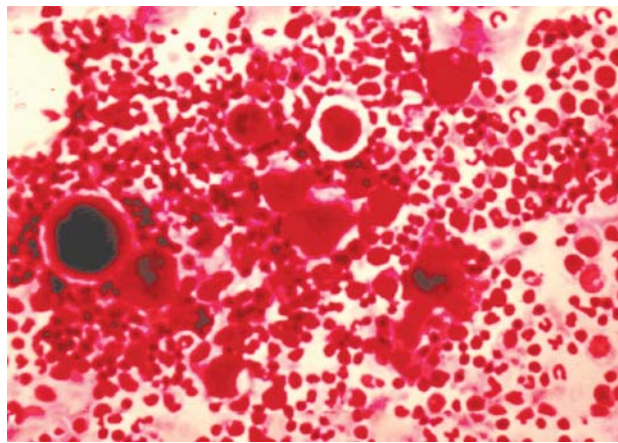


Fig. 32.31: Immune thrombocytopenic purpura. Note increased megakaryocytes in bone marrow.

Treatment

Acute ITP

Management consists of minimizing the risk of severe bleeding by an initial limitation of activity. Active bleeding should be controlled. Drugs like aspirin and antihistaminics which have antiplatelet function should be avoided. Platelet transfusions are reserved for severe bleeding not responding to drug therapy. In such cases large doses of platelets are required.

Various forms of corticosteroids—prednisolone, methylprednisolone and other drugs like intravenous immunoglobulin (IVIG) and anti Rh globulin (anti D) have been used to raise the platelet counts. However, the drugs have not consistently been proven to be of value in moderate or mild thrombocytopenia. Opinions differ, but there is general agreement that children with platelet count less than 20,000/mm³ or having significant mucosal bleeding (and ICH) should be given drugs (Box 32.10).

Chronic ITP

Most cases with chronic ITP have mild to moderate thrombocytopenia and cutaneous or occasional mucosal bleeding. Such cases do not require much treatment. Only cases with persistently severe thrombocytopenia is less

Box 32.10 Pharmacotherapy of ITP

IVIG, 1 g/kg/day for 1 or 2 days or 400 mg/kg/day for 5 days

– OR –

Anti D-immunoglobulin, 50–75 mg/kg

– OR –

Prednisolone, 2 mg/kg/day for 2–4 weeks. An initial high dose has been used (4 mg/kg/day for two days). After completion of the course, it is tapered

– OR –

Dexamethasone, 20 mg/m² over 4 days every 3 weeks for 4–6 weeks

– OR –

Methylprednisolone, 30 mg/kg/day for three days.

Abbreviation: ITP, immune thrombocytopenic purpura.

than 20,000/mm³ or with significant mucosal bleed need to be treated. For such cases various forms of therapy have been used.

Methylprednisone (30 mg/kg/day for 3 days followed by 30 mg/kg for one day every month);

High dose dexamethasone (20 mg/m²/day for 4 days every month for 6 months). Long term low dose steroids, IVIG, intravenous anti-DIG have been used with variable results. Doing splenectomy in children with chronic ITP is a difficult decision. Splenectomy has been successful in two-third of the patients, but as more long term follow up data is accumulating, many cases with initial response have relapsed.

Refractory ITP

The cases persisting with thrombocytopenic after splenectomy are called **refractory ITP**. Such cases are difficult to treat. The options include vincristine, cyclophosphamide, cyclosporine, interferons, colchicine, azathioprine, danazol, dapsone, high dose vitamin C anti-CD20 antibody, plasmapheresis, rituximab, thrombopoietin receptor binding agents, etc. Recently, in adults an association with *Helicobacter pylori* infection has been demonstrated and improvement in platelet count is reported after its eradication.

Prognosis

The conservative measures lead to recovery in 85–90% cases within 6 months. The remaining 10–15% pass into the chronic phase. In the latter, recovery may be expected in about 75% following splenectomy; the rest show lessening of the manifestations.

NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

Definition

Neonatal alloimmune thrombocytopenia (NAT) is defined as a “destruction of the fetal platelets by maternal antibodies against paternally inherited platelet antigens (HPA-1a or HPA-5b) which are present on fetal platelets”.

Clinical Features

Clinical features in symptomatic neonates include ICH immediate (within hours) of birth.

Diagnosis

Diagnosis is by high index of suspicion and exclusion of other causes of thrombocytopenia such as sepsis, meconium aspiration and intrauterine infections Toxoplasmosis, other agents, rubella, cytomegalovirus and herpes simplex (TORCH). In sick neonates and maternal SLE in healthy-looking neonate.

Treatment

It comprises of transfusion of well-irradiated, washed maternal platelets.

Prevention

For subsequent pregnancies (in which risk of overt disease increases), serial ultrasound examination of the growing fetus for ICH is indicated. Additionally, oral steroids (dexamethasone or betamethasone) plus IVIG, 1 g/kg/dose every 4 weeks during pregnancy and at birth are recommended.

WISKOTT-ALDRICH SYNDROME (WAS)

This is an X-linked recessive disorder, characterized by a triad of eczema, thrombocytopenic hemorrhagic diathesis and immunodeficiency leading to enhanced vulnerability to infections.

The disorder represents a unique state in which thrombocytopenia results from abnormal platelet formation or release in spite of adequacy in number of megakaryocytes. Many megakaryocytes are, however, of bizarre morphology. The platelets are reduced in number and half of the normal size. They also have decreased number of alpha granules, dense bodies and mitochondria. Further, they are less aggregatable and suffer from abnormalities of energy metabolism.

A small proportion of patients (5%) develop lymphoreticular malignancies. At present, treatment of choice is splenectomy. A significant improvement in thrombocytopenia follows this intervention. In view of enhanced risk of fulminant sepsis, it is mandatory to give prophylactic penicillin to the patients who undergo splenectomy. A small proportion of cases may respond to transfer factor or bone marrow transplantation.

DRUG-INDUCED THROMBOCYTOPENIA

Drugs such as sulfas, co-trimoxazole, chloramphenicol, carbamazepine and diphenylhydantoin (phenytoin) may occasionally cause thrombocytopenic purpura. The modus operandi is either a megakaryocyte insult or an immune-mediated process in which the drug acts as a hapten. Withdrawal of the offending agent reverses the abnormality.

HENOCH-SCHÖNLEIN PURPURA

(Anaphylactic Purpura, Allergic Non-thrombocytopenic Purpura)

Henoch-Schönlein purpura (HSP), one of the most common vasculitis disorders, is far less frequent than the ITP.

Definition

HSP is a non-thrombocytopenic purpura characterized by vasculitis and presenting with widespread purpuric lesions (particularly urticaria-like skin eruptions) with involvement of the joints (Schönlein purpura) and/or abdominal viscera (Henoch purpura). Progressive renal involvement carries bad prognosis.

Etiology

In all probability, it is a collagen disorder. A preceding infection (say GAS) is often believed to be responsible for it.

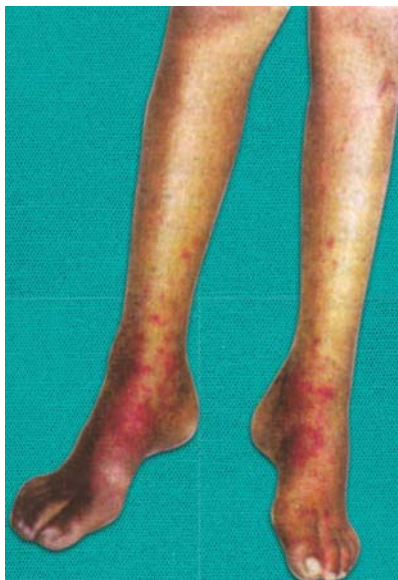


Fig. 32.32: Henoch-Schönlein purpura. Note the ecchymotic patches. Arthritis of knees and ankles was present. The presenting reason for hospitalization was colicky abdominal pain with vomiting. Hemogram was essentially normal.

Clinical Features

Henoch purpura is dominated by signs of acute/surgical abdomen. At times the picture almost mimics intestinal obstruction, volvulus, intussusception or appendicitis. Abdominal pain is usually colicky and frequently accompanied by vomiting.

Schönlein purpura is dominated by signs of arthritis or arthralgia, especially of the knees and ankles (Figs 32.32 and 32.33). Often, it has been mistaken for rheumatic or rheumatoid arthritis. Acute glomerulonephritis may be associated with this variety.

Most common manifestation is purpuric skin rash, especially over the extensor aspects of the legs and buttocks. In some cases, rash may be urticarial, macular, papular, or maculapapular. Manifestations pertaining to the vasculitis of kidneys, GIT, cardio vascular system (CVS), respiratory tract or CNS may be present subsequently.

Diagnosis

HSP is by and large a clinical diagnosis.

- Hematological investigations reveal normal results with no thrombocytopenia in particular.
- *Streptococcus hemolyticus* may be cultured from throat swab.
- Antistreptolysin O (ASO) titer may be raised.
- Ultrasound abdomen for excluding any surgical condition causing severe abdominal pain.
- In case of involvement of the kidneys, urine shows varying degree of albumin, red cells and casts.
- Intravenous pyelogram (IVP) may show poor functioning and the renal biopsy changes of glomerulonephritis.

Complications

- **Short-term**
 - Acute glomerulonephritis



Fig. 32.33: Henoch-Schönlein purpura. Note the petechiae and purpura.

- Acute kidney injury
- GI hemorrhage
- Guillain-Barre syndrome
- CNS vasculitis—ICH
- Pulmonary hemorrhage
- Carditis
- Epididymorchitis
- **Long-term**
 - Chronic renal failure
 - Nephrotic syndrome
 - End-stage renal disease (ESRD).

Treatment

It is a self-limiting vasculitis. However, rest, adequate nutrition and symptomatic treatment are required as and when indicated. Acute renal failure warrants therapy as in acute glomerulonephritis. Indications for steroid therapy include:

- Life-threatening intestinal hemorrhage, obstruction, perforation or intussusception.
- CNS involvement.

Prognosis

A vast majority of the children with HSP recover completely in 4–6 weeks. Children who do not recover in 4–6 weeks may go into a chronic phase. Mortality is usually from renal failure, or cerebral or gastrointestinal bleeding.

PURPURA FULMINANS

This is a rare life-threatening condition characterized by acute infarction (hemorrhage) of skin (Figs 32.34A and B) that accompanies or follows bacterial (*Staphylococcus aureus*, *Hemophilus influenzae*, *Klebsiella*, *Pseudomonas aeruginosa*, *Neisseria meningitidis*) or viral (chickenpox, URI) infection.



Figs 32.34A and B: Purpura fulminans. Note the purpura with hemorrhagic infarcts.

Exact pathogenesis is unclear. A close resemblance to Schwartzman reaction is, however, known. Hematologic picture is that of DIC. Management includes supportive therapy, treatment of shock, antibiotics to control the causative infection or to prevent secondary infection, and heparin and steroids in combination or alone.

LEUKOCYTE DYSFUNCTION

Opsonization is the remarkable ability of the neutrophils to recognize foreign antigen through humoral factors (opsonins) like heat stable IgG antibodies and heat stable complement C3b. Dysfunction in opsonization and phagocytosis may cause a number of disorders such as Chediak-Higashi syndrome chronic granulomatous disease and neutropenia.

Chediak-Higashi syndrome, an autosomal recessive disorder of progressive multifocal leukoencephalopathy PML function, is characterized by recurrent infections, oculocutaneous albinism, neutropenia and, occasionally, hepatosplenomegaly, lymphadenopathy and lymphoid infiltration of tissues mimicking ALL.

Chronic granulomatous disease, an X-linked disorder, is characterized by inability to kill bacteria, resulting in recurrent bacterial infections of skin, lymphadenopathy, poor healing, hepatosplenomegaly, multiple liver abscesses, pneumonia, diarrhea, conjunctivitis, otitis media, sinusitis, osteomyelitis, etc.

Neutropenia is characterized by PML count is less than $1500/\text{mm}^3$ and may be congenital (cyclic neutropenia, chronic benign neutropenia) or acquired (leukemia, lymphoma, and solid tumors).

NEUTROPENIA

An absolute fall in the number of circulating neutrophil in blood may range from mild to profound (Table 32.9).

Table 32.9: Classification of neutropenia

Classes	Ranges
Mild	$1001-1500/\text{mm}^3$
Moderate	$501-1000/\text{mm}^3$
Severe	$<500/\text{mm}^3$
Profound	$<100/\text{mm}^3$

Box 32.11 Major types of neutropenia

Defects of uncommitted stem cells

- Reticular dysgenesis
- Cyclic neutropenia
- T and B lymphocyte disorders

Defects of committed stem cells

- Chronic benign neutropenia without infection
- Severe familial neutropenia
- Chediak-Higashi syndrome
- Cartilage hair dysplasia
- Shwachman-Diamond syndrome

Acquired disorders

- **Myelofibrosis:** Leukemia, lymphoma, solid tumors, Gaucher disease, osteopetrosis, radiation
- **Infections:** HIV, HB, rubella, RSV, varicella, influenza, *Salmonella*
- **Drugs/chemicals:** Chemotherapy for malignancy, heavy metals, benzene-containing organic compounds.

Abbreviations: HIV, human immunodeficiency virus; HBV, hepatitis B virus; RSV, respiratory syncytial virus.

Etiology

Box 32.11 gives the three major types of neutropenia depending on etiology.

Febrile Neutropenia

Development of unexplained fever in a majority of the subjects with malignancy is secondary to neutropenia as a result of certain infections which may be viral (hepatitis, HIV, respiratory syncytial virus (RSV), varicella, rubella, influenza), bacterial (*Salmonella*, *Staphylococcus aureus*, *Streptococcus*, *Mycoplasma tuberculosis*, *Brucella*, *Listeria*), fungal (*Candida*, *Aspergillus*, *mucormycosis*) and parasitic. Since febrile neutropenia is almost silent because of suppression of manifestations of infection, it can be quite life-threatening.

Clinical Features

The most frequent sites of serious infection are blood, lungs, soft tissues and mucosal surfaces (gingivitis, mucositis), GIT (esophagitis, typhilitis with right lower quadrant abdominal pain and a lump, anorectal infections).

Diagnosis

Since classic signs and symptoms of infection are likely to be missing, a high index of suspicion is the benchmark for diagnosis of febrile neutropenia. Besides special sensitivity to subtle manifestations of infection, investigations should include CBC, differential blood count, platelet count, LFT, renal function tests, blood cultures for both aerobic and anaerobic pathogens and aspiration or biopsy for bacterial, fungal, mycobacterial and viral strains and cultures.

660 Management

Initial empirical therapy consists of parenteral combination chemotherapy, e.g. a third generation cephalosporin plus an aminoglycoside/a beta-lactam antimicrobial agent, ceftazidime plus amikacin, vancomycin alone. Duration of chemotherapy should be till the resolution of neutropenia or for a period of 14 days.

Persistence of fever despite the initial empirical therapy is an indication for modifying the initial therapy plus introducing an antifungal agent (amphotericin B). Hematopoietic growth factors (stem cell growth factors: G-MCSF, G-CSF, granulocyte transfusion; monoclonal antibodies, interleukin, interleukin receptor antagonists, interferon, cytokines) may be employed to boost the host defenses as adjuvant to antimicrobial therapy.

Prevention

It comprises of:

- **Isolation techniques:** High efficiency particulate air (HEPA) filtered room, neutropenia precautions (gloves, masks, mopping rather than brushing, soft tooth brush. Low microbial diet, hand washing).
- Prophylactic antibiotics, including fungal prophylaxis with nystatin. Clotrimazole, amphotericin B or fluconazole.

THROMBOTIC DISORDERS

Thrombotic disorders are much less frequent in childhood than in adults. Peak incidence is in infancy and adolescence. Morbidity and mortality is high.

Etiopathogenesis

Predisposing factors include frequent use of central venous catheter (CVC), congenital heart disease, malignancy, chemotherapy, total parenteral nutrition (TPN), obesity, sickle cell disease, liver disease, sepsis and nephrotic syndrome (Box 32.12).

Furthermore, pediatric thrombosis may have risk factors in the form of inherited prothrombotic disorders e.g. Factor V Leiden, protein C deficiency, protein F deficiency, antithrombin deficiency, protein S deficiency, antithrom-

Box 32.12 Risk factors for pediatric thrombosis

- Dehydration and dyselectrolytemia
- Congenital heart disease, e.g tetralogy of Fallot
- Central venous catheter
- Nephrotic syndrome
- DIC
- Sepsis
- Recent surgery
- Trauma
- Drugs: Steroids and L-asparaginase therapy in ALL
- Antiphospholipid antibody syndrome*.

Abbreviations: DIC, disseminated intravascular coagulation; ALL, acute lymphoblastic leukemia.

* Also termed Hughes syndrome, it is an autoimmune, hypercoagulable state caused by antiphospholipid antibodies. APS provokes blood clots (thrombosis) in both arteries and veins.

bin deficiency, prothrombin gene C20210A mutation. Elevated lipoprotein (a) level, hyperhomocysteinemia, resistance to activated protein C, etc.

Clinical Features

- **Deep vein thrombosis:** Painful swelling and discoloration of the affected limb, inguinal or abdominal pain, fever, malfunctioning of the CVC and evidence of collateral circulation.
- **Arterial thrombosis:** Cool limbs, diminished or absent peripheral pulses.
- **Pulmonary embolism:** Dyspnea, chest pain (pleuritic), cough, fever, tachypnea, anxiety.
- **Renal vein thrombosis:** Hematuria, pain in flank.
- **CNS thrombosis:** Lethargy, vomiting, seizures, weakness in a limb.
- **Stroke:**
 - **In children:** Headache and hemiplegia.
 - **In utero:** Seizures and drowsiness.

Diagnosis

Hematological studies include PT, APTT, fibrinogen and platelet count, D-dimer test (more important as a predictive test than a diagnostic test; it is a sensitive indicator of underlying DIC), anticardiolipin antibodies, LA and tests for inherited prothrombin defects.

Venogram is the gold standard for diagnosing equivocal cases and thrombosis involving upper limbs. **Color Doppler/duplex ultrasound** is quite dependable for diagnosis of thrombosis of lower limbs and distal veins of upper limbs. For diagnosis of pulmonary embolism, **ventilation/perfusion (V/Q) scan** and **spiral CT** scans are employed.

Treatment

The cornerstone of treatment of venous thrombosis is standard heparin as such or in conjunction with AT-III. Thrombolytic agents (urokinase, streptokinase and recombinant plasminogen activator) are used to cause rapid clot lysis, resulting in prompt lysis of the obstruction. Oral anticoagulants (Warfarin) are good for long term anticoagulant therapy.

Prognosis

If anticoagulation therapy is not up to the mark, risk of recurrent thrombosis remains. Though it is just around 5% without risk factors, in patients with risk factors it zooms to as high as 20% (one risk factor) to 50% (two risk factors).

POLYCYTHEMIA (Erythrocytosis)

Polycythemia, a Greek term, signifies an increase above the normal in the number of red cells in the blood, usually accompanied by an increase in the hemoglobin level and packed red cell volume.

Primary Polycythemia

It may be of two types.

1. **Polycythemia vera (PV)**, a chronic myeloproliferative disease characterized by hyperplasia of the marrow,

excessive red cell production, high blood viscosity and hemorrhagic tendencies, is seldom seen in childhood.

2. **Benign familial polycythemia** or **primary erythrocytosis** is the most common type seen in pediatric practice. It is transmitted as an autosomal dominant (occasionally autosomal recessive) trait.

Manifestations include headache, lethargy, plethora and splenomegaly. RBC count may be as high as 10 million/mm³ with a hemoglobin of 27 g/dL and hematocrit of 80%. The treatment of choice is phlebotomy.

Secondary Polycythemia

It results in response to a hypoxic state that causes poor oxygen saturation of blood. Thus, it may occur in cyanotic congenital heart disease, chronic pulmonary disease such as cystic fibrosis, pulmonary arteriovenous fistula or cavernous hemangioma of the lung, gross obesity as in Pickwickian syndrome, methemoglobinemia, sulfhemoglobinemia and in subjects living at high altitude.

Nonhypoxic causes of secondary polycythemia include renal and brain tumors, hydronephrosis, Cushing disease, cobalt therapy and rare hemoglobinopathies. Some polycythemia is a normal observation in newborns; it may be particularly exaggerated in a twin, in a preterm or small-for-dates infant, in an infant of a diabetic mother, and in babies suffering from Down syndrome and congenital adrenal hyperplasia. **Relative polycythemia** may result from dehydration such as occurring in gastroenteritis, in stress, in hypertension and in diuretic therapy. Severe polycythemia may cause hemorrhagic defects such as thrombocytopenia, DIC and increased anti-coagulants with high fibrinolytic activity.

Treatment of secondary polycythemia consists of correction of the cause. If that is not possible or if polycythemia is quite severe, treatment of choice is phlebotomy and/or isovolumetric exchange transfusion to restore the hematocrit to normal limits.

BLOOD COMPONENT THERAPY

Whole blood transfusion is indicated in only blood loss with hypovolemic shock. However, appropriate blood component should be employed for specific conditions.

Classification

- Unmodified
 - **Cellular:** Packed RBCs, platelets, granulocytes
 - **Plasma:** Fresh frozen plasma, cryoprecipitate, factor components
- Modified
 - **Irradiated:** RBCs, platelets and granulocytes
 - **Leukocyte depleted:** RBCs and platelets
 - **Saline washed:** RBCs and platelets.

Unmodified Components

Packed RBCs

Here some of the plasma is removed from whole blood. For improvement of oxygen carrying capacity in chronic anemia with hypoxic manifestations as also CCF, this is the

best product. Dose is 10 mL/kg over 3–4 hours. A transfusion of 3 mL/kg increases Hb concentration by around 1 g/dL.

Indications

- Neonates
 - Physiologic anemia of infancy/anemia of prematurity
 - Hb is less than 10 g/dL if symptomatic
 - Hb is less than 13g/dL in cardiopulmonary disease
 - Hb is less than 10 g/dL in FTT
 - Replacement of iatrogenic blood loss
 - Situations requiring large volume transfusions, e.g. exchange transfusion.
- Infants and older children
 - Hb is less than 7 g/dL, symptomatic anemia
 - Blood loss due to hemorrhage.

Platelets

Indications

- Platelet count is less than $50 \times 10^9/L$ in premature infants
- Platelet count is less than $5 \times 10^9/L$ in active bleeding major invasive or surgical procedure
- Platelet count is less than $20 \times 10^9/L$ in marrow failure
- Minor surgical procedure
- Cardiovascular bypass/extracorporeal membrane oxygenation (ECMO) with excessive hemorrhage
- ITP.

Dose

0.1 unit/kg raises platelet counts by 30,000/mm³.

Granulocytes

Indications

- Neonatal sepsis with meningitis, septic shock or necrotizing enterocolitis.
- Absolute neutropenia is less than 3×10^9 PMN cells/mm³ during first week, less than 1×10^9 PMN cells/mm³ thereafter.

Dose

$1-2 \times 10^9$ granulocytes/kg BW (10–15 ml/kg BW) every 24 hours.

Fresh Frozen Plasma (FFP)

It is the fluid portion of the blood unit that is centrifuged, separated and frozen at less than (-30°C) within 6 hours of collection.

Indications

- Severe hemorrhagic disease of the newborn (HDN) with vitamin K dependent coagulopathy
- Replacement of isolated factor deficiencies in the absence of specific component therapy
- DIC
- Replacement therapy in antithrombin III, protein C or S deficiency
- Reversal of hemostatic disorders in dilutional coagulopathy from massive transfusion
- Reversal of adverse effects in a baby born to the mother on such agent as phenobarbital or phenytoin
- Thrombotic thrombocytopenic purpura (TTP) for therapeutic plasma exchange

- 662** ■ Coagulopathy due to drug (L-asparaginase) therapy
- Invasive procedures provided that PT and/or PTTK are quite high (1–1.5 times than normal).

Dose

10 mL/kg BW over 1–2 hours, to be repeated every ½ hour until hemorrhage is controlled.

Cryoprecipitate

Cryoprecipitate is obtained by thawing FFP at 4°C. It provided fibrinogen, F VIII, F vWF and F XIII 5 times as high as in FFP.

Indications

- Classical hemophilia (factor VIII deficiency) when factor concentrates are not available von Willebrand disease
- Congenital factor XIII deficiency
- Congenital hypofibrinogenemia
- Acquired hypofibrinogenemia secondary to DIC and ECMO
- As fibrin sealant in preparing fibrin glue.

Dose

20 mL/kg is suggestive.

Modified Components

Gamma-irradiated Blood Products

Indications

The aim of gamma-irradiation is to prevent graft-versus-host disease (GVHD) due to the immune response mounted by the donor T-lymphocytes against host tissues.

- Severe immunodeficiency
- Intrauterine or extrauterine transfusions
- Transfusions from first degree relatives with threat of GVHD.

Dose

25–30 Gy or more.

Saline Washed RBCs

Indications

- Prevention of urticarial reactions in hypersensitivity to plasma
- Prevention of anaphylaxis in IgG deficiency
- Prevention of nonhemolytic febrile transfusion reactions in thalassemia subjects receiving multi-transfusions
- Removal of complement in paroxysmal nocturnal hemoglobinuria.

Saline Washed Platelets

These are beneficial in severe allergic reactions to blood transfusion and in neonatal alloimmune thrombocytopenia.

BONE MARROW TRANSPLANTATION (Hematopoietic Stem Cell Transplantation)

The term, *stem cell*, refers to the cell that has an extensive self-maintaining (self-renewal) capacity extending throughout the entire lifespan of the organism.

HSCT is transplantation of hematopoietic progenitor cells from bone marrow, peripheral blood or umbilical cord in order

to reconstitute the bone marrow. HSCT may prove life-saving for a number of malignant and nonmalignant disorders that are otherwise fatal in due course of time. Bone marrow, umbilical cord blood and cytokine-mobilized peripheral blood are the currently employed sources of stem cells.

Types

When the cells are taken from the same individual, it is called *autologous*. When the donor is another individual, it is termed *allogeneic*, the donor may be a human leukocyte antigen (HLA)-matched sibling or an unrelated individual. *Syngeneic* HSCT means that the stem cell is obtained from identical twin (Box 32.13).

Indications

This new therapeutic modality, now available in India, may be indicated in several situations, provided that alternative therapeutic modalities are not able to offer reasonable chance for a cure or prolongation of survival (Box 32.14).

Box 32.13 Types of HSCT

- **Syngenic HSCT:** When stem cell is obtained from identical twin.
- **Allogenic HSCT:** When stem cell is obtained from a HLA matched sibling.
- **Autologous HSCT:** When normal appearing marrow is obtained from the patient himself on cytotoxic drugs.

Abbreviations: HSCT, hematopoietic stem cell transplantation; HLA, human leukocyte antigen.

Box 32.14 Indications of Hematopoiesis stem cell transplantation

Nonmalignant hematological disorders

- Aplastic anemia
- Fanconi anemia
- Blackfan-Diamond syndrome
- Hemoglobinopathies
 - Thalassemia major
 - Sickle-cell anemia.

Hematological malignancies

- Leukemias
 - Acute myeloid leukemia
 - Acute lymphoblastic leukemia
 - Chronic myeloid leukemia.

Nonhematological malignancies

- Lymphomas
 - Hodgkin, lymphoma
 - Non-Hodgkins lymphoma
- Multiple Myeloma
- Myelodysplastic syndromes
- Solid tumors
 - Neuroblastoma
 - Wilms tumor
 - Retinoblastoma
 - Brain tumors: Gliomas
 - Ewing sarcoma.

Miscellaneous

- Immunodeficiency syndromes
 - SCID
 - CGD
 - Wiscott-Aldrich syndrome
 - Chédiak-Higashi syndrome
- Inborn errors of metabolism.

Abbreviations: SCID, severe combined immunodeficiency; CGD, chronic granulomatous disease.

Procedure

An essential prerequisite is that the recipient must receive conditioning pretransplant immunosuppression with cyclophosphamide and low dose total body radiation to cut down risk of graft rejection or GVHD.

Bone marrow is obtained from multiple sites on the posterior iliac crest, using sterile technique, under general anesthesia. Just 200 mL is enough in children. It is filtered to obtain a single cell suspension and to remove particles that can possibly embolize to the lungs. The suspension is transfused IV to the recipient.

Hyperalimentation (parenteral) is advisable during the first month after transplant to prevent malnutrition and to improve survival. During this period, transplant patient frequently develops anorexia, nausea, vomiting and other symptoms related to GIT as a result of chemotherapy, radiation and GVHD. He/she is particularly vulnerable to

develop infection and bleeding during this period of severe bone marrow aplasia. Effective supportive measures are, therefore, mandatory.

Complications

The complications of the procedure include:

- Graft rejection
- GVHD
- Superadded infections (e.g. interstitial pneumonia)
- Recurrence of leukemia in ALL.

Outcome

It depends on:

- Stage of the disease at the time of transplantation
- Cytogenic abnormalities
- Technique of HLA matching
- Detection of superimposed infections and their therapy

Multiple Choice Questions

1. Hair-on-end appearance in X-ray of skull may be seen in each of the following, except:
 - A. Megaloblastic anemia
 - B. Thalassemia major
 - C. Iron deficiency anemia
 - D. Sickle-cell anemia
2. Microcytic hypochromic anemia is seen in each of the following, except:
 - A. Thalassemia major
 - B. Iron deficiency anemia
 - C. Lead toxicity
 - D. G6PD deficiency
3. True observations about immune thrombocytopenic purpura include all except:
 - A. An immunological reaction to a recent infection
 - B. Occurrence of bleeding from multiple sites
 - C. Splenomegaly is a common finding
 - D. Response to IVIG is better than to steroids
4. In thalassemia intermediate, hematological findings other than microcytic-hypochromic anemia that help in differentiation from IDA include each of the following, except:
 - A. Target cell
 - B. Near normal red cell count
 - C. Basophilic stippling
 - D. Normal or high serum ferritin levels
5. Spot the wrong observation:
 - A. Serum iron less than 30 mg/dL and ferritin less than 10 ng/dL are considered diagnostic of iron deficiency anemia
 - B. Sideroblastic anemia is characterized by iron resistance, hypochromia, high serum iron and overloaded iron stores
 - C. The nomenclature, hemorrhagic disease of the newborn, is now replaced by the term vitamin K deficiency bleeding (VKDB)
 - D. Von Willebrand disease is an autosomal recessive disorder that behaves in the same way as classical hemophilia A
 - E. Refractory immune thrombocytopenic purpura (ITP) means persistence of thrombocytopenia even after splenectomy

Answers

1. A 2. D 3. C 4. A 5. D

Clinical Problem-solving

Review 1

A 17-year-old vegetarian girl presents with progressive pallor, low-grade fever, generalized weakness, glossitis with cracked tongue, hyperpigmented knuckles and terminal phalanges and numbness of fingers and toes. Spleen just palpable (size grade 2). Liver palpable 2 cm (span 13 cm).

1. What is most likely clinical diagnosis?
2. How do you justify low-grade fever?
3. Mention a laboratory investigation that may clinch the diagnosis.
4. What should be the therapeutic approach?

Review 2

A 2-year-old malnourished child weighing 9 kg presents with severe abdominal colic. Examination reveals moderate pallor, dactylitis and hepatosplenomegaly (liver span 8 cm, spleen size grade 3).

1. What is the most probable diagnosis?
2. How will you confirm the diagnosis?
3. Any role of hydroxyurea?
4. Any curative therapy?

Answers

Review 1

1. Megaloblastic anemia in all probability due to vitamin B₁₂ deficiency as such or along with folate deficiency.
2. Megaloblastic anemia being a panmyelopathy makes the patient vulnerable to infections resulting from neutropenia.
3. Bone marrow showing characteristic megaloblasts.
4. Vitamin B₁₂ 1000 µg/day (IM) once or twice a week, preferably with folic acid, 5 mg orally daily for 6–8 weeks.

Review 2

1. Sick cell “crisis” presenting as a surgical emergency.
2. Demonstration of sickle-shaped RBC is virtually diagnostic. In addition, there is an increase in osmotic fragility. Electrophoresis shows that 50–100% hemoglobin is HbS though an increase in HbF is also present.
3. Yes, in a proportion of cases, hydroxyurea is of value in raising HbF and reducing frequency and severity of crisis as also blood transfusion requirements.
4. Only bone marrow transplantation may prove curative.

FURTHER READING

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1. Gupte S. *Recent Advances in Pediatrics (Special Vol. 7: Hematology)*. New Delhi: Jaypee 1999.

INTRODUCTION

Pediatric cancer is rare. Nevertheless, it is an important cause of morbidity and mortality. With the availability of advanced diagnostic techniques and improved therapeutic and supportive care, cure rate in childhood cancer has considerably improved. Around 60–70% of pediatric cancer is now curable. In some malignancies, cure rate has reached as high as 90%.

According to a conservative estimate, nearly 50,000 children suffer from cancer every year. In terms of frequency, **leukemias** (33%) top the list followed by **brain tumors** (20%) and **lymphoma** (12%). These three malignancies together, therefore, account for a vast majority of the pediatric cancers in India.

LEUKEMIA

Leukemia is characterized by persistent and enormous production of immature white cells. It is responsible for an overwhelming majority of the childhood malignancies. The incidence of leukemia in various pediatric centers in India varies from 0.3–1.2%.

About 98% children suffering from leukemia have acute type of the disease. Mostly it is acute lymphoblastic leukemia (ALL) which accounts for 76% of the cases. Acute nonlymphocytic leukemia (ANLL) is responsible for 20% and chronic myelogenous leukemia (CML) and others together for a meagre 4%.

Box 33.1 presents categorization of leukemias and Table 33.1 gives French-American-British (FAB) classification of ALL. Immunologic classification of ALL is given in Box 33.2. Chronic leukemia is uncommon in childhood. Chronic lymphocytic leukemia (CLL) is particularly very rare in pediatric practice. CML, adult or juvenile type, is, of course, occasionally encountered.

Another important feature of childhood leukemia is the **aleukemic leukemia** in around half of the cases. In this form, total leukocyte count (TLC) is either normal or low. Down syndrome, Klinefelter syndrome, Fanconi anemia and some other syndromes/conditions are known for vulnerability to higher risk of acute leukemia.

Etiology

It is as yet unknown in most cases. Factors which enhance the risk of leukemia and may even play an etiological role include:

Box 33.1 Categories of childhood leukemia

ALL

- Standard-risk ALL (Null cell)
- High risk ALL
 - T Cell ALL
 - B Cell ALL.

ANLL

- M1 (myeloblastic, no maturation)
- M2 (myeloblastic, some maturation)
- M3 (hypergranular promyelocytic)
- M4 (myelomonocytic)
- M5 (monocytic)
- M6 (erythroleukemia).

CML

- Adult form
 - Chronic phase
 - Blast crisis
- Juvenile form—congenital leukemia.

Abbreviations: ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphoblastic leukemia; CML, chronic myelogenous leukemia.

Table 33.1: FAB classification of acute lymphoblastic leukemia

Feature	L ₁	L ₂	L ₃
Cell size	Small	Large heterogenous	Large homogenous
Nuclear chromatin	Homogenous	Variable heterogenous	Finely stippled homogenous
Nuclear shape	Regular occasional cleft	Irregular with cleft and indentation	Regular and round
Nucleoli	Absent	One or even more	One or even more
Cytoplasm	Scanty	Variable	Moderately abundant
Basophilic cytoplasm	Slight	Variable	Quite deep
Cytoplasmic vacuolation	Variable	Variable	Prominent

Abbreviation: FAB, French-American-British.

- Genetic syndromes/conditions (Box 33.3)
- Exposure to adverse influences
 - Ionizing radiation
 - Viral particles
 - Parental smoking

Box 33.2 Immunological classification of acute lymphoblastic leukemia

B cell precursors

- Stem cell
- Early pre B cell–cytoplasmic Ig negative (clg –). These cells often express the CD 19 and CD 10
- Pre B cell–cytoplasmic Ig positive (clg +). Mature B cell whose hallmark is slg +ve
- CD 10 is found in 80% of all null cell leukemias.

T cell precursors

- Stem cell
- Early (Stage 1) intrathymic differentiation; most T cell leukemias arise from this stage
- Intermediate (Stage 2)
- Late (Stage 3).

Abbreviations: CD, cluster of differentiation; IG, immunoglobulin.

Box 33.3 Congenital/hereditary conditions associated with increased risk of leukemias

- Down syndrome (10–20 times more chances of ALL and AML)
- Ataxia telangiectasia
- Congenital X-linked immunodeficiency
- Fanconi anemia
- Bloom syndrome
- Kostmann syndrome
- Klinefelter syndrome
- Neurofibromatosis
- Immunodeficiency
- Ataxia telangiectasia.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

- Therapeutic irradiation
- Chemotherapy (cyclophosphamide, nitrogen mustard)

■ Pesticides.

ACUTE LYMPHOBLASTIC LEUKEMIA

Clinical Features

Acute leukemia is a great imitator. The clinical presentation may be vague and varied, resembling almost any disease. In ALL, the peak incidence occurs in the first 5 years of life, particularly in 2–5 years age group. The second peak occurs between 8 and 10 years of age. Tables 33.1 and Box 33.2 give FAB and immunological classifications of ALL respectively.

The onset is acute or insidious. The initial manifestations may include progressive pallor, anorexia, weakness, fever, malaise, lymphadenopathy, hepatosplenomegaly, purpura, nasal bleed, black eye etc (Fig. 33.1). Bone or joint pains and, occasionally, swelling with or without sternal tenderness, hematemesis, melena, hematuria and sores in mouth are the other common presenting features. At times, excessive bleeding after a minor operation like dental extraction or a minor injury may be the first alarm-



Fig. 33.1: Acute lymphoblastic leukemia. Note the black eye. The patient had severe anemia, sternal tenderness, generalized lymphadenopathy and hepatosplenomegaly. Bone marrow was full of “blast” cells.

ing manifestation. Leukemic infiltration of skin may cause pea-sized papules. Occasionally, arrhythmias with heart block may occur.

Central nervous system (CNS) involvement leads to meningeal leukemia. It may present with headache, vomiting, drowsiness or unconsciousness, convulsions or cranial nerve involvement. Cerebrospinal fluid (CSF) shows increased proteins, low sugar and pleocytosis. Even blast cells may be seen.

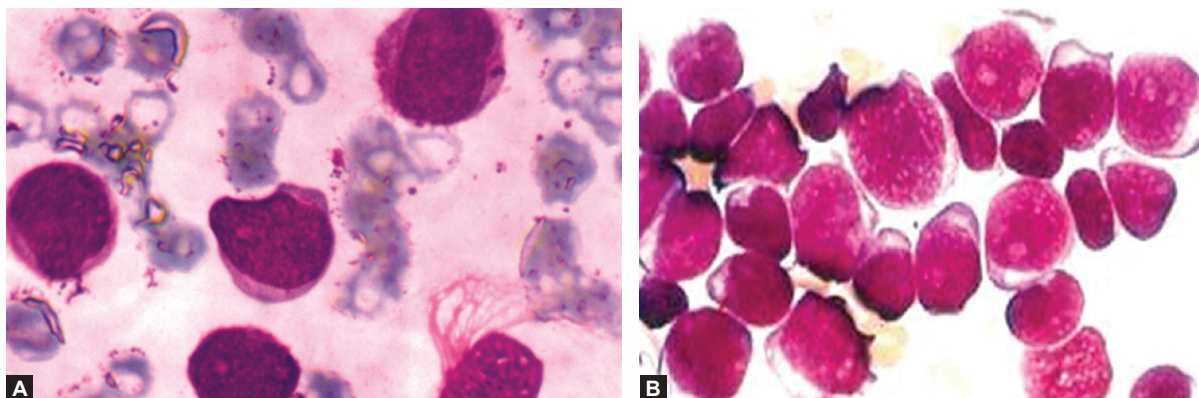
In **congenital leukemia**, an infant with a chromosomal abnormality (trisomy 21 in particular) is born with hepatosplenomegaly, petechiae, ecchymoses, cutaneous nodules and CNS involvement, leucocytosis with immature myeloid forms, and thrombocytopenia. Differential diagnosis is from neuroblastoma, leukemoid reaction (erythroblastosis fetalis, severe congenital infections) and myeloproliferative disorders occurring in trisomy 21 or chromosome 21 mosaicism.

Diagnosis

The characteristic laboratory findings are:

- Moderate to severe anemia
- Thrombocytopenia
- Total leukocyte count under $3,000/\text{mm}^3$. In 1/4th cases, platelet count may exceed $100,000/\text{mm}^3$ and TLC more than $50,000/\text{mm}^3$ *
- Demonstration of primitive cells (blast cells) gives a definite clue to the diagnosis. This, however, needs confirmation from bone marrow which is likely to be nearly completely replaced by leukemic lymphoblasts (Figs 33.2A and B). A needle biopsy of marrow may be needed in some cases for this purpose.
- Chest X-ray for a mediastinal mass and lumbar puncture (LP) for leukemic cells are useful investigations.

* Leukemoid reactions occurring in various conditions like Gram-negative septicemic, enteric fever and miliary tuberculosis should be ruled out. Blast cells are never seen in these diseases.



Figs 33.2A and B: Bone marrow in ALL. Note the large number of blast cells and reduced bone marrow elements.

Treatment

The most effective regimen at present available for the most common form of ALL, **null cell ALL** or **standard-risk ALL**, is given in Table 33.2. This gives remission in about 95% of the ALL subjects with the following features:

- Age over 2 years and under 10 years
- TLC under 100,000/mm³
- No mediastinal mass
- No CNS involvement
- Blast cells without B or N cell features.

In **T cell ALL**, relapse usually occurs within 2 years with the regimen given in Table 33.2. Patient may benefit considerably from bone marrow transplantation, or from measures-under-trial such as more intensive multidrug

regimens, purged autologous marrow before infusion, adenosine deaminase inhibitor, and deoxycoformycin.

In **B cell ALL**, where prognosis is worst, chemotherapy has got to be more intensive though short (3–6 months). With the very intensive regimen (same as for advanced B cell lymphoma), cure rates have dramatically shot up to 75% from the earlier 20% or so. Bone marrow transplantation should seriously be considered. Administration of recombinant human granulocyte-macrophage colony stimulating factor (G-CSF), available as Leucomox, 5–10 µg/kg/day subcutaneously (SC) for 7–10 days beginning after the remission-induction chemotherapy is just over, or until the postnadir neutrophil count is 1,000/mm³ or higher for 2 days may benefit some cases.

As and when relapse occurs, irrespective of the type of standard-risk or high-risk ALL, it is in the form of CNS leukemia and/or testicular enlargement. This is an indication for irradiation, intensification of systemic treatment and CNS therapy.

Prognosis

In the standard-risk or null cell ALL, remission occurs in 95%; 75% remain in remission for at least 5 years, and majority are cured. In B cell ALL, 95% do attain remission, but only 60% are able to maintain it beyond 5 years. Cure is rare. In T cell ALL, cure may occur in only a minority of the sufferers.

Among the factors contributing to relatively poorer prognosis in India are:

- Poor compliance/high dropout rate because of financial burden
- High incidence of superadded infections
- Lack of availability of good supportive care
- Poor tolerance of chemotherapy by malnourished children
- High component of T cell leukemia and cytogenetic abnormalities (known for poor outcome) in Indian children with ALL.

ACUTE NON LYMPHOBLASTIC LEUKEMIA (ANLL)

Clinical Features

In ANLL the presenting features include rapidly progressive pallor, fever, active bleeding, bone pain,

Table 33.2: Currently recommended treatment regimen for low-risk ALL

Remission induction chemotherapy (4–6 weeks)

This is achieved by intensive systemic chemotherapy.

- Vincristine 1.5 mg/m² (maximum 2 mg) IV once a week
- Prednisolone 40 mg/m² (maximum 60 mg) orally daily
- Asparaginase 10,000 Units/m²/day IM bi-weekly

Intrathecal CNS prophylaxis with triple therapy

- **Methotrexate (MTX)**
 - Under 1 year 10 mg
 - 2–8 years 12.5 mg
 - Over 9 years 15 mg
- **Hydrocortisone (HC)**
 - Under 1 year 10 mg
 - 2–8 years 12.5 mg
 - Over 9 years 16 mg
- **Cytosine arabinoside**
 - Under 1 year 20 mg
 - 2–8 years 25 mg
 - Over 9 years 30 mg

Systemic continuation/maintenance therapy

- 6 MP 50 mg/m²/day orally
- MTX 20 mg/m²/week orally, IV, IM
- Pulse of MTX ± 6 MP given at higher doses
- This therapy is continued for 2.5 to 3 years

Reinforcement/late intensification therapy

- Vincristine 1.5 mg/m² (maximum 2 mg) IV every 4 weeks
- Prednisolone 40 mg/m²/day orally for 7 days every 4 weeks, Once a week during induction and then every 8 week for 2 years

Abbreviations: CNS, central nervous system; ALL, acute lymphoblastic leukemia; IV, intravenous; IM, intramuscular; MP, mercaptopurine.

668 gastrointestinal tract (GIT) upset and gingival swelling from infiltration with leukemic cells. Preceding these manifestations, some subjects may complain of fatigue and recurrent infections over a period of year or so. Signs include hepatosplenomegaly, marked lymphadenopathy and, in some cases, joint pains and also CNS findings. Leukemic infiltration may cause proptosis.

Diagnosis

Diagnostic profile is virtually on the same lines as in ALL. When cytology is consistent with ANLL of type M3, a coagulogram must be done for disseminated intravascular coagulation (DIC) and as baseline parameters for future reference.

Treatment

In ANLL, over 70% of cases shows remission with cytosine arabinoside continuous intravenous (IV) infusion for 7 days and IV daunorubicin for 3 days. Maintenance therapy is with rotating combinations of several drugs for up to 2 years. CNS prophylaxis with intrathecal triple therapy is indicated. In M3 type of ANLL, fatal hemorrhage from DIC is expected. Heparin therapy is, therefore, needed.

In juvenile type, treatment is on the lines of that of ANLL. Results are, however, discouraging.

Prognosis

30–40% subjects may be cured.

CHRONIC MYELOID LEUKEMIA (CML)

Clinical Features

In CML (adult type), onset is insidious with progressive enlargement of spleen (massive splenomegaly) which may become firm and reach into the pelvis (Fig. 33.3). Most cases occur around 10–12 years of age.

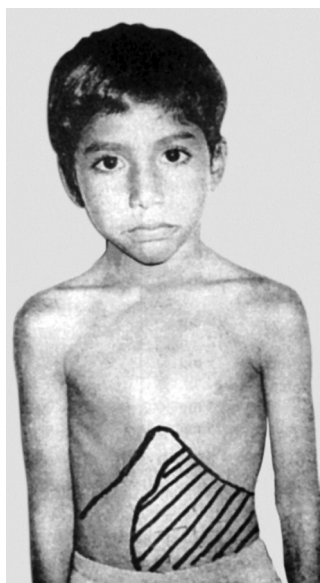


Fig. 33.3: Massive enlargement of spleen in chronic myeloid leukemia.

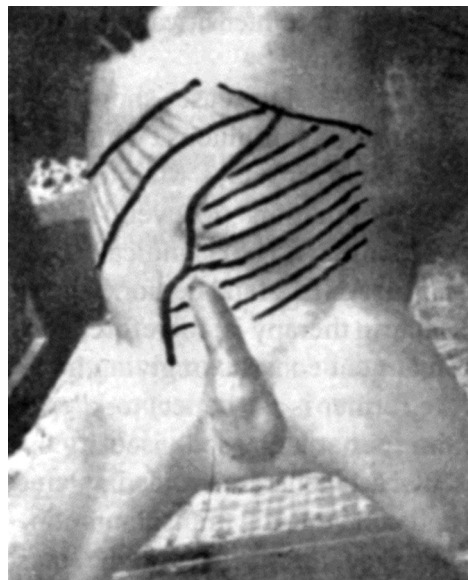


Fig. 33.4: Chronic myeloid leukemia. Note gross splenohepatomegaly and priapism.

Treatment

Treatment consists of giving hydroxyurea or busulfan (the former is far better) to keep TLC under 100,000/mm³ so that increased viscosity of blood and cerebrovascular accidents are avoided, splenic radiation, interferon and bone marrow transplantation.

Prognosis

In CML, no recorded cure is known as at present.

CONGENITAL LEUKEMIA

For control of high TLC, single agent chemotherapy and for control of bleeding, platelet transfusions are sufficient. Spontaneous remission in the first few weeks is possible.

In CML (juvenile type), occurring in children under 2 years, manifestations include eczema, lymphadenopathy, recurrent bacterial infections and hepatosplenomegaly (Fig. 33.4).

LYMPHOMAS

The term, *lymphomas*, refers to a group of disorders in which there is a dominant malignant involvement of the lymphoid tissue with progressive anemia and fever. Currently, two major types of lymphomas are recognized, namely:

1. Hodgkin lymphoma (60%)
2. Non-Hodgkin lymphoma (40%)

The two types together are the third most common cause of childhood malignancy (after leukemias and brain tumors). However, they have almost entirely different clinical presentations, treatment and prognosis.

HODGKIN LYMPHOMA (HL)

The disease is uncommon in childhood. It is however, known to have occurred at as young an age as 3 years. Peak

Table 33.3: Histological types of Hodgkin lymphoma

Histological type	Features
Hodgkin lymphoma with nodular lymphocytic predominance	Frequency 10%; outcome excellent
Classical Hodgkin lymphoma	
• Nodular sclerosis	Frequency 20-50%; outcome very good
• Mixed cellularity	Frequency 20-40%
• Lymphocyte rich	Frequency 5-10%; outcome good
• Lymphocyte depletion	Frequency 5-15%; outcome poor

incidence in childhood is seen in adolescence around 15 years of age.

Etiopathology

Hodgkin lymphoma is twice as common in boys as in girls.

- It has occurred in like-sex siblings.
- It has been postulated that some viral etiology may well be in operation in causation of Hodgkin disease.

Histological Types

The lymphoma arises in T dependent areas of the lymphoid tissue. The so-called **Reed-Sternberg cell** is the central histological feature. The origin of the cell appears to be from an antigen presenting cell of the mononuclear phagocyte reticulum cell lineage, possibly from interdigitating reticulum cell.

Depending on the histological features, classical HL has been classified into four types as shown in Table 33.3. The types which are most commonly seen in pediatric practice are nodular sclerosis and mixed cellularity, the former in the second decade whereas the latter in the first decade of life.

Clinical Features

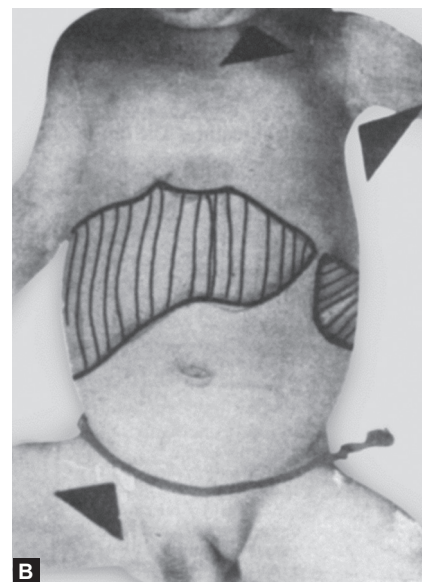
Painless enlargement of lymph glands, usually unilateral cervical, is the most common presenting feature. The involved glands are usually matted, firm or rubbery, nontender and mobile (Figs 33.5A and B).

With progression of the disease, deeper glands may also be involved. They may cause symptoms by compression on other structures. Chronic whooping type of cough and manifestations due to mediastinal compression in the form of respiratory distress are well known. General symptoms include fever, anorexia, loss of weight, night sweats and pruritus. The so-called **Pel-Ebstein fever** occurs only in a small proportion (10–15%) of the cases. Ingestion of alcohol may cause abdominal pain. Box 33.4 gives the clinical staging of the disease.

Diagnosis

Mandatory

- Hematologic investigations usually show anemia, high erythrocyte sedimentation rate (ESR) and eosinophilia.
- X-ray studies are of value to evaluate the glands in the mediastinum and abdomen.



Figs 33.5A and B: Hodgkin lymphoma. (A) Note the matted, mobile and nontender cervical lymphadenopathy; (B) The child presented with fever (intermittent), predominantly cervical lymphadenopathy, hepatosplenomegaly and mild ascites.

- Computed tomography (CT) scan of neck, chest and abdomen.
- Biopsy from a lymph node or extra-nodal structure is most useful.
- Bone marrow should be done to exclude its involvement.

Optional

- CT scan brain
- Positron emission computed tomography (PECT)
- Bone scan.

Box 33.4 Modified Ann Arbor clinical staging system for Hodgkin's lymphoma

Stage	Characteristics
I	Involvement of a single lymphatic gland region (I) or a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph gland regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (IIE)
III	Involvement of glands in regions on both sides of diaphragm (III) or localized involvement of an extralymphatic organ or site (IIIE) or spleen (IIIE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph gland involvement. The organs involved should be identified by a symbol: IV A = Asymptomatic IV B = Fever (>38°C, sweating, weight loss above 10% of body weight) IV X = Bulky tumor (>10 cm diameter, mediastinal mass occupying 1/3rd of the maximum transverse intrathoracic diameter).

Once diagnosis has been reached, laparotomy is a rule in almost all cases. At laparotomy, several abdominal lymph gland biopsies, liver biopsy and splenectomy are done.

Treatment

Today the treatment of choice is a combination of irradiation and aggressive chemotherapy.

- **Stage Ia or IIa:** Field irradiation or irradiation of clinically involved areas plus chemotherapy
- **Stage Ib or IIb:** Field irradiation followed by 6 months chemotherapy
- **Stage IIIa:** 3 cycles of chemotherapy, then total gland irradiation followed by chemotherapy for a total of 9 months
- **Stage IIIb or IV:** 12 courses of chemotherapy plus irradiation to areas of bulk disease.

Two widely-accepted chemotherapy regimens are: **MOPP** employing Mustard (nitrogen mustard), Oncovin (vincristine), Procarbazine and Prednisone; or **COPP** employing Cyclophosphamide, vincristine, Procarbazine and Prednisone and **ABVD** employing Adriamycin (doxorubicin), Bleomycin, Vinblastine and Dacarbazine.

Prognosis

With modern treatment employing both chemotherapy and radiation, prognosis has considerably improved. A large majority of the children with stage I and II are cured. About 75% of children in stage III are cured. Over 50% of children in stage IV are cured with intensive chemotherapy. Complications of the treatment are:

- **Irradiation**
 - Restriction of lung capacity
 - Cardiac involvement
 - Late hypothyroidism

- Retardation in growth of the vertebral column
- Sterility
- Premature menopause
- Retardation in growth of breasts.

■ Chemotherapy

- Late pulmonary toxicity (bleomycin)
- Late cardiac toxicity (doxorubicin)
- Sterility in the male (MOPP).

■ Surgery

- Overwhelming sepsis
- Abdominal adhesions
- Secondary malignancy (leukemia).

NON-HODGKIN LYMPHOMA (NHL)

The entity includes a diverse group of malignancies involving the lymphoid organs.

Etiopathology

Burkitt's lymphoma, also called *African lymphoma*, predominantly a disease of Central Africa and Uganda, seems to be secondary to Epstein-Barr virus (EBV) though herpes group virus and reovirus type 3 have also been incremented. An insect vector—possibly a mosquito—plays a role in its transmission. The role of immunologic disturbances in the causation of NHL is currently receiving attention.

Clinical Features

Acute abdomen is the most common presentation since the single most frequent site of origin of lymphoma is the lymphoid tissue of the GIT, usually in the ileocecal region. Extra-abdominal presentation is generally in the form of nontender enlargement of the lymph nodes. Manifestations due to compressions, including that of mediastinum and spinal cord, are common.

Presenting features of Burkitt's lymphoma include jaw tumors, abdominal lumps and proptosis. Lymphadenopathy is conspicuous by its absence. Box 33.5 gives the clinical staging of the NHL.

Diagnosis

Non-Hodgkin lymphoma is a very fast growing tumor. Hence, prompt diagnosis is mandatory for appropriate chemotherapy and good prognosis. Clinical and laboratory work-up of the case should be on similar lines

Box 33.5 St Jude's clinical staging system for NHL

Low-risk (Localized)

- **Stage I:** One single site
- **Stage II:** Two or more sites on the same side of the diaphragm

High-risk (Advanced)

- **Stage III:** Disseminated disease without involvement of bone marrow or CNS
- **Stage IV:** Any of the above with involvement of bone marrow or CNS.

Abbreviations: CNS, central nervous system; NHL, non-Hodgkin lymphoma.

Box 33.6 Laboratory work-up in NHL

- CBC
- Serum electrolytes, including uric acid, lactate dehydrogenase, creatinine, calcium and phosphorus
- LFT
- Chest X-ray and CT scan
- Abdominal and pelvic ultrasonography/ CT scan
- Bone scan/gallium scan
- Bone marrow (both aspiration and biopsy)
- CSF (cytology in particular).

Abbreviations: CBC, complete blood count; LFT, liver function test; CT, computed tomography; CSF, cerebrospinal fluid; NHL, non-Hodgkin lymphoma.

as for Hodgkin's disease (Box 33.6). However, it is a must to do LP in each and every case. Routine laparotomy and splenectomy are not needed.

Treatment

The treatment of choice is a combination of irradiation and aggressive chemotherapy. The use of methotrexate and cranial irradiation prior to clinical involvement of the CNS is presently strongly advocated.

For localized nodal disease (stage I), treatment of choice is on the lines of ALL. However, only 1 year course is recommended. For B cell type (Burkitt lymphoma histology), a combination of high dose methotrexate and cyclophosphamide is recommended. It should be intensive therapy given for only 1 year. For primary intrathoracic tumors in stage III, best cure rate is obtained with intensive 10-drug regimen. T cell lymphoma requires CNS prophylaxis with chemotherapy, irradiation or both with a maintenance for 1 year.

Prognosis

Lymphoma with isolated glandular or intestinal involvement, provided that mediastinum is spared, has a good prognosis. Relapses with involvement of marrow and CNS are quite uncommon once the disease has been brought under control for 2 years or more.

Response of Burkitt lymphoma to chemotherapy (methotrexate for early and cyclophosphamide for advanced stage) is extremely favorable. Radiation and surgical excision of 90% of the tumor mass improve the remission and disease-free survival. Cure rate in stages I and II is 90% and in stages III and IV is 50%.

In subjects who had a relapse, use of intensive chemotherapy followed by autologous marrow reinfusion of identical twin marrow transplantation may prove of value. Prognosis is worse in situations where bone marrow involvement and/or leukemic conversion have occurred.

WILMS' TUMOR**(Nephroblastoma)**

It is by and large next only to neuroblastoma in frequency of occurrence among the solid tumors of infancy and childhood. Embryonal in origin, this tumor develops within the kidney parenchyma, distorting it and invading the surrounding tissues. Existence of certain congenital anomalies predisposes to its development (Box 33.7)

Box 33.7 Accompaniments of Wilm's tumor

- Ambiguous genitalia
- Undescended testes
- Hypospadias
- Duplication of ureter or kidney
- Horse-shoe kidney
- Aniridia
- Hemihypertrophy
- Beckwith syndrome.

Clinical Features

The most important presenting feature is a large unilateral abdominal mass (Fig. 33.6). Often, it is detected by the doctor on routine examination. But, more frequently, it is noticed by the parents while dressing or undressing the child. Pain abdomen is infrequent. Hematuria is rare.

If metastases have occurred, associated symptoms will be seen depending on the organ(s) involved. Almost half of the sufferers older than 2 years show metastases. About one-fourth under 2 years too have some metastases. Once in a while the tumor may rupture from injury. In such a situation, the child presents as an acute surgical emergency. Bilateral tumor is infrequent, the incidence being just 2%. Box 33.8 presents clinical staging of Wilms' tumor.

Diagnosis

- As soon as Wilms' tumor is clinically suspected, take a plain X-ray film of abdomen. It shows a soft tissue opacity displacing the gut in the area normally occupied by the kidney.
- An intravenous pyelography (IVP) showing distortion of calyces by a mass within the kidney confirms the diagnosis.
- Urinalysis may reveal hematuria.
- Bone marrow may rarely show metastases.
- Chest X-rays should also be taken to detect any metastases in the lungs.



Fig. 33.6: Wilms' tumor.

Box 33.8**Clinical staging for Wilms' tumor (NWTs Group)**

- **Stage I:** Limited to the kidneys; can be fully excised with capsular surface intact
- **Stage II:** Extends beyond the kidney but can be fully excised
- **Stage III:** Residual nonhematogenous extension of the tumor, confined to the abdomen following surgery
- **Stage IV:** Hematogenous metastases, most frequently involving the lung
- **Stage V:** Bilateral kidney involvement in 5–10% cases.

Abbreviation: NWTs, National Wilm's Tumor Study.

Treatment

If the tumor is grossly resectable, especially in a child under 2 years of age, treatment consists of surgery plus actinomycin-D and vincristine over several months.

In the event of metastases or extensive local extension, irradiation is added to the surgery and chemotherapy is given for longer periods. Addition of doxorubicin to chemotherapy gives yet more favorable results. For stage IV, radiotherapy and combination therapy with 3 or more drugs for 15 months is currently recommended. Preoperative therapy is recommended only in stage V to cause shrinkage of the primary tumor so that partial nephrectomy, salvaging as much residual normal kidney as possible, could be carried out.

Prognosis

With aggressive treatment, 75–90%, 2 year disease-free survival rate has been attained. Prognosis is better when Wilms' tumor is diagnosed before the age of 2 years and when its weight is under 250 g. Recurrence carries bad prognosis.

NEUROBLASTOMA

It is a malignant tumor arising from sympathetic ganglia or adrenal medulla. The common locations of neuroblastoma are the abdomen and chest. Early metastasis constitutes the hallmark of the disease.

Clinical Features

The peak incidence occurs at 2–3 years of age. It is rare to encounter it after the age of 6 years. Of course, there are recorded cases at any time from neonatal period to adolescence. Familial occurrence is recorded; so is the occurrence in identical twins.

The most common presenting feature is a palpable mass in the abdomen. The mass is hard, fixed, crosses the midline and pushes the kidney upwards. The rest of the manifestations depend on the extent of the disease. Fever, bone pain, anemia and loss of weight are common presenting complaints. Subcutaneous nodules, adrenal masses with involvement of the marrow, hepatomegaly from massive infiltration of liver, paraplegia, paroxysmal hypertension and proptosis secondary to retro-orbital deposits are the other manifestations. Evans clinical staging of neuroblastoma is given in Box 33.9.

Box 33.9**Evans clinical staging system for neuroblastoma**

- **Stage I:** Tumor confined to organ or structure of origin
- **Stage II:** Tumor extending in continuity beyond organ or structure of origin, but not crossing the midline; regional nodes on homolateral side may be involved
- **Stage III:** Tumor extending in continuity beyond the midline; original nodes may be involved bilaterally; bilateral extension of midline disease
- **Stage IV:** Remote disease involving selection, organs, soft tissue, distant nodes, and so on
- **Stage V:** Patients who would otherwise be stage I or II, i.e. with small and/or resectable primary tumor, but who have remote disease confined only to one or more of the following sites: liver, skin or bone marrow (not bone).

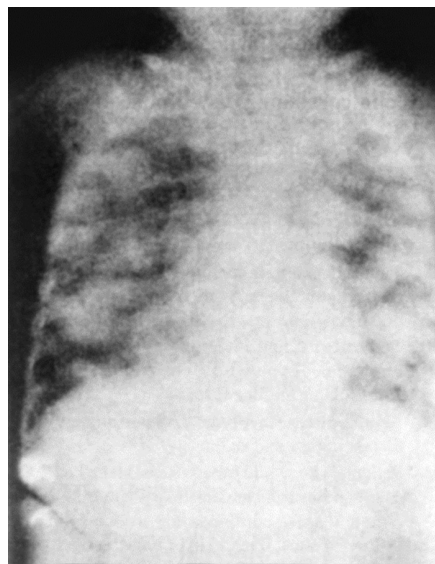


Fig. 33.7: Neuroblastoma. Note multiple secondaries in lungs.

Diagnosis

- X-ray studies reveal displacement of one of the kidneys by a suprarenal mass and/or a paravertebral shadow or a tumor in the posterior mediastinum. Gross metastases in the lung may also be detected (Fig. 33.7).
- CT scan is the best for abdominal tumor and of considerable help in defining the extent of intraspinal extension.
- Urine examination reveals an excess excretion of catecholamine and/or their metabolites, vanillylmandelic acid (VMA) and cystyithionine.
- Bone marrow may show secondary deposits, i.e. neuroblasts, which may simulate leukemia.

Treatment

Treatment involves a combined application of surgery, irradiation and chemotherapy with drugs like vincristine, cyclophosphamide, decarbazine and doxorubicin. VM26, epipodophyllotoxins or cisplatin may be given.

Since most tumors have had dissemination at the time of diagnosis, chemotherapy is the cornerstone of treatment. With the following two regimens, 50% of the patients undergo remission:

1. Cyclophosphamide
 - Doxorubicin
2. VM26
 - Cisplatin
 - Etoposide

Response to bone marrow transplantation, autologous marrow reinfusion after purging with cyclophosphamide derivatives, is being studied.

Prognosis

Age has considerable bearing on the prognosis. If diagnosed after the age of 2 years, death occurs rapidly in over 80% of the cases despite adequate therapy. Around 80% or more with 2 year disease-free survival with therapy has been reported under one year of age.

Serial measurement of VMA in urine provides a good index of response to therapy. Spontaneous cure has also been on record.

TUMORS OF LIVER

Two well-known primary tumors of liver are—*hepatoblastoma* and *hepatocarcinoma* (hepatoma).

Hepatoblastoma

Though quite infrequent, hepatoblastoma is still relatively more common than the other primary tumor of the liver, i.e. hepatocarcinoma (hepatoma). It usually occurs in male children under 3 years of age and involves predominantly the right lobe of the liver. Boys and girls ratio is 1.5: 1.

Clinical Features

Manifestations include noticeable abdominal distention with or without pain, anorexia, weight loss, anemia, fever and fatigue. Less frequent manifestations are vomiting, jaundice and, in boys, virilization. Hepatomegaly with or without a definable tumor mass is present (Fig. 33.8).

Investigations

- Liver function tests are only slightly affected. Cystathioninuria and raised alpha-fetoglobulin may be demonstrated.
- Plain X-ray abdomen and IVP assist in establishing intrahepatic origin of the lump.
- Specialized techniques such as scans, angiography and CT may be of considerable help in the diagnostic work-up.
- Liver biopsy may be done, but the final tissue diagnosis should be made at laparotomy.

Treatment

Treatment is radical excision of the involved lobe and isolated lung metastasis. Chemotherapy (cisplatin, vincristine, adriamycin) has a temporary, beneficial effect.

Prognosis

As a rule, prognosis has so far been disappointing. Mortality rate is 65%. Liver transplantation may improve prognosis.

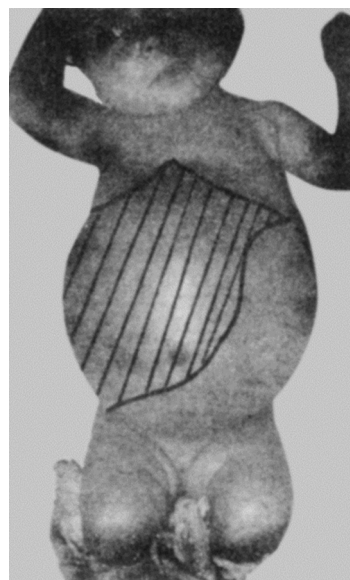


Fig. 33.8: Hepatoblastoma.

BRAIN TUMORS

Overview

Next to leukemias, brain tumors constitute the most common malignancy of childhood.

Manifestations

A vast majority of them are infratentorial and close to mid-line. Hence, hydrocephalus is a common finding. Vomiting, headache, papilledema, ataxia, diplopia and personality changes in the form of behavior problems, speech disturbances, irritability and decline in intellect are other frequent accompanying manifestations.

Investigations

Skull X-ray often shows sutural diastasis and silver-beaten appearance (Fig. 33.9). CT scan has been a tremendous advance in localization of the brain tumors.



Fig. 33.9: Skull X-ray, showing silver-beaten appearance in a child with brain tumor.



Fig. 33.10: Medulloblastoma. Note the sutural diastasis as a result of Intracranial space-occupying lesion (ICSOL).

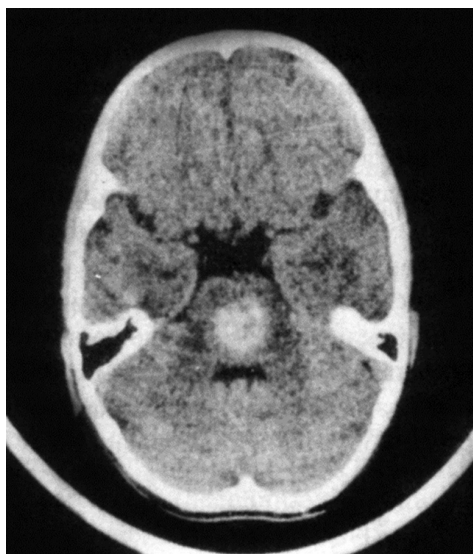


Fig. 33.11: Medulloblastoma. CT scan showing medulloblastoma which is the most common posterior fossa tumor after astrocytoma (cerebellar) and the most common in under age 7 years.

INFRATENTORIAL BRAIN TUMORS

Cerebellar Tumors

Astrocytoma occurs in 3–8 years age group and is characterized by unilateral cerebellar signs such as ataxia, nystagmus, hypotonia, areflexia and tilting of the head to the side of the lesion. It is relatively slow growing and is amenable to surgical excision.

Medulloblastoma (Figs 33.10 and 33.11) occurs in 3–5 years age-group, most often in boys. Ataxia, usually truncal, is severe and common. It is rapid growing and highly malignant. Treatment is in the form of irradiation, surgery and chemotherapy.

Brainstem Tumors

Pontine glioma (Fig. 33.12) occurs in 6–8 years age group. Bilateral multiple cranial nerve involvement (usually sixth and seventh), ataxia, pyramidal signs and absent or minimal signs of raised intracranial tension are its characteristic features. It is fast growing and amenable to irradiation.

Fourth Ventricle Tumor

Ependymoma occurs usually in the age group of 7–10 years. Its characteristic features include local extension, early rise in intracranial tension, subarachnoid hemorrhage, cranial nerve palsies, pyramidal signs and calcification. Only radiotherapy is possible.

SUPRATENTORIAL BRAIN TUMORS

These include **gliomas** of optic pathway, hypothalamus and cerebral hemisphere, papilloma of choroid plexus, ependymoma of cerebral hemisphere, dermoid and teratoma of midbrain and craniopharyngioma. Common presenting features of supratentorial tumors are convulsions and hemiparesis.

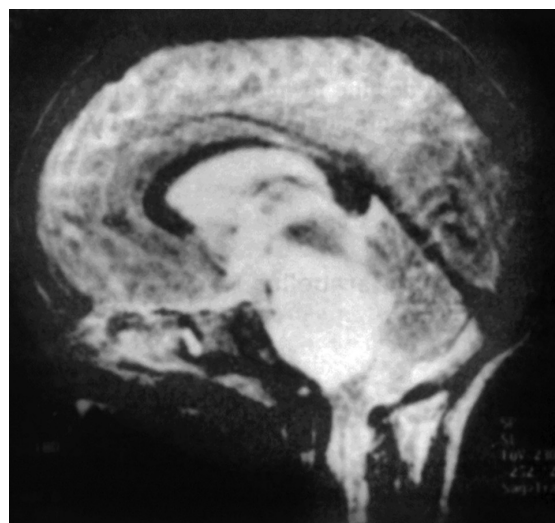


Fig. 33.12: Glioma. Magnetic resonance imaging of a solid brainstem glioma which is the third most common posterior fossa tumor of childhood.

Craniopharyngioma originates from cell rests of Rathke's pouch and occurs at all ages. Clinical features include raised intracranial tension, growth failure with dwarfism, bitemporal hemianopia, visual field loss, diabetes insipidus, delayed puberty, calcification in suprasellar or sellar region and ballooning of sella in X-ray skull. The tumor is frequently benign. Treatment is surgical excision with hormonal therapy, or drainage of the cyst and radiotherapy.

BONE TUMORS

Bone tumors in children, almost always either osteosarcoma or Ewing sarcoma (the latter is by and large limited to white population), have a tendency to occur in adolescents rather than young children. Chondrosarcoma is rare in children.



Fig. 33.13: Alopecia secondary to chemotherapy for osteosarcoma.

OSTEOSARCOMA

Osteosarcoma characteristically occurs during the adolescent spurt (the mean age being 15 years) and involves metaphyseal ends of long bones like femur, tibia and humerus.

Predisposing Factors

Predisposing diseases include retinoblastoma, multiple osteochondromatosis (Ollier disease), multiple hereditary exostosis, osteogenesis imperfecta, Paget disease and Ewing tumor.

Clinical Features

Manifestations include pain at the site of the tumor, localized swelling and warmth, limitation of movements, limp, tenderness and erythema. Metastasis may lead to respiratory embarrassment, pleural effusion, pneumothorax and other signs and symptoms depending on the sites.

Diagnosis

Diagnosis should be suspected in every patient with unexplained bone pain in association with a palpable mass.

- X-ray shows sclerosis and new bone formation.
- CT scan of the affected bone delineates the magnitude of the medullary involvement. CT scan of the chest becomes mandatory particularly in cases where no metastasis has been seen on chest X-ray.

Treatment

Treatment is radical surgery followed by aggressive chemotherapy employing high dose methotrexate, cisplatin, doxorubicin, bleomycin, cytoxan and dactinomycin. This provides 80% disease-free survival compared to just 20% with surgery alone. On an average, 50–60% survival is reported. Fig. 33.13 shows severe alopecia in a child on chemotherapy for osteosarcoma.

EWING SARCOMA

Ewing tumor characteristically occurs in later childhood and adolescence, involving either long bones of extremities

(most often femur) or flat bones of head and trunk. It is rare in nonwhite races.

Clinical Features

Manifestations include painful swelling with constitutional symptoms like fever and malaise. This presentation may well initially give the clinician an impression of osteomyelitis or eosinophilic granuloma.

Diagnosis

Diagnosis is supported by:

- X-ray showing mottled, lytic, onion-skin pattern must be confirmed by surgical bone biopsy showing round cell tumor.
- CT scan is required to define the magnitude of the tumor.
- For lung metastases, chest X-ray and CT scan, for bone metastases, radionuclide bone scan, and for bone marrow metastases, marrow biopsy are needed.

Treatment

It consists of high dose irradiation of the primary tumor site and combination of chemotherapy employing vincristine, cyclophosphamide, dactinomycin and doxorubicin. With metastases, survival is 5–15%. Without metastasis it is around 60%.

SOFT TISSUE SARCOMAS

Rhabdomyosarcoma

It is the most common among the multitude of soft tissue sarcomas in various tissues of origin (examples: primitive sarcoma; fibrous-fibrosarcoma; lymphatic-lymphangiosarcoma; blood angiosarcoma; synovium-synovial cell sarcoma; smooth muscle-desmoid; striated-muscle rhabdomyosarcoma).

The tumor shows an early peak before 5 years and a later peak around 15–19 years of age. In the first peak, head, neck, prostate, bladder and vagina are involved. In the second peak, genitourinary tract is the major site. Neurofibromatosis and cancer families predispose to rhabdomyosarcoma.

Clinical Features

Manifestations include a lump (may be painful) with complaints referable to the organ/system involved. For instance, if the location is nasopharynx, manifestations may be nasal congestion, mouth-breathing, epistaxis and swallowing and chewing difficulties. Involvement of the larynx causes croupy cough and progressive stridor.

In orbital involvement, there is proptosis, ptosis, periorbital edema, change in visual acuity and local pain. A rapidly growing scrotal mass may mean paratesticular tissue involvement. Because of early metastasis, bone and lung symptoms are common denominators of rhabdomyosarcoma in any location.

Diagnosis

Diagnosis is confirmed by X-ray and CT scan studies as well as tumor tissue and bone marrow.

Table 33.4: IRS staging and treatment of rhabdomyosarcoma

Group	Features	Treatment
I	Localized disease; regional nodes not involved; with chemotherapy completely removable	Complete local excision with chemotherapy
II	Grossly resected tumor with regional nodes involved on microscopic residual disease	Surgery followed by local irradiation and chemotherapy
III	Gross residual disease	Same as for group II
IV	Distant metastatic disease	Chemotherapy

Abbreviation: IRS, International Rhabdomyosarcoma Study.

Treatment

Treatment varies with the International Rhabdomyosarcoma Study (IRS) staging as shown in Table 33.4.

Rhabdomyosarcoma in locations which are parameningeal, irrespective of group, is an indication for IT therapy. With suitable treatment, 80–90% subjects have tumor-free survival in Groups I and II. In Groups III and IV, it is 60–65%. In older children, prognosis is worse than in younger children.

RETINOBLASTOMA

This rare tumor, though the most common ocular neoplasm of childhood, usually develops in the posterior portion of the retina. About 70% subjects have unilateral (Fig. 33.14) and 30% bilateral disease. Average age for unilateral disease is 26 months and for bilateral disease 8 months. Around 90% of cases are less than 5 years of age.

Predisposing Factors

All children with bilateral disease and 10–20% with unilateral disease have a genetic predisposition. The retinoblas-

toma gene is located on chromosome 13. This gene carries risk of osteosarcoma and a secondary malignancy like a pineal tumor, the so-called *trilateral retinoblastoma*.

Clinical Features

Manifestations include leukocoria, yellow white reflex in the pupil, loss of vision, squint, pain, pupillary irregularity, or hyphema. In advanced cases, frank proptosis, raised intracranial pressure (ICP) and bone pain may be present. Metastasis is rare.

Diagnosis

Diagnosis is by demonstration of yellow white reflex on fundoscopy in cases of leukocoria. CT scan is needed to determine extent of tumor as also if optic nerve and bony structures are involved. Other investigations should include a skeletal survey, radionuclide bone scan of the head, CSF, bone marrow, carcinoembryonic antigen and alpha-fetoproteins.

Treatment

Treatment in unilateral disease is usually enucleation of the eye. In bilateral disease, attempt is made to save at least one eye with useful vision by radiotherapy. In gross or microscopic disease in the enucleated eye and in widespread metastatic disease, chemotherapy with cytoxan and doxorubicin should be considered. With appropriate treatment, recovery in early diagnosed cases is 90–100%.

THYMOMA

This anterior mediastinal soft tissue tumor is rare in childhood. It rarely metastasizes outside chest (Fig. 33.15).

Clinical Features

Manifestations include compression symptoms like intractable cough, dyspnea, dysphagia and prominence of the vein of the chest wall and neck due to superior vena cava compression. Elevated production of suppressor

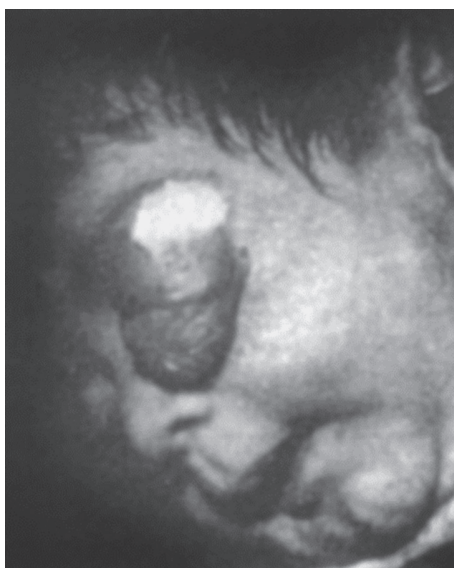


Fig. 33.14: Unilateral retinoblastoma.



Fig. 33.15: Thymoma.



Fig. 33.16: Teratoma. Resection revealed varied contents such as hair follicles and dental, bony and visceral tissue.

lymphocytes by the tumor may cause imbalance in immune regulation, leading to paraneoplastic syndromes such as myasthenia gravis, pure red cell aplasia and hypogammaglobulinemia.

Treatment

Though it is a radiosensitive tumor, the treatment of choice is complete surgical excision. Recurrences need to be treated with chemotherapeutic agents such as doxorubicin, cyclophosphamide and cisplatin.

TERATOMAS

- These are a kind of germ cell tumors, occurring most often in infants (usually female) in sacrococcygeal region (Fig. 33.16).
- Alpha-fetoprotein (AFP) may be normal or just slightly high. Significant elevation in this marker points to development of malignancy in the teratoma (Fig. 33.17).
- Risk of malignancy is 10% in infants under 2 months, but 50% in those above 4 months.
- Treatment is surgical excision. Cure rate is around 75–90%.

ONCOLOGICAL EMERGENCIES

Definition

The term, **oncological emergency**, is applied to an acute and potentially life-threatening event, directly or indirectly related to the neoplasm or its treatment. Emergencies can be encountered in two ways such as:

1. Initial/during as a result of oncological condition per se
 - Compression or invasion of a vital organ such as trachea, esophagus or superior vena cava by a solid tumor
 - Compromised function of heart or lung by an effusion in pericardium or pleural cavity



Fig. 33.17: Sacrococcygeal teratoma.

- Cerebral edema and raised ICP by metastasis into brain
 - Spinal cord compression by a malignancy
 - Anemia, bleeding, thrombosis, cerebrovascular episodes and infections secondary to thrombocytopenia and coagulation defects from invasion of the bone marrow
 - Hormonal problems secondary to paraneoplastic secretions
 - Metabolic emergencies.
2. As a result of aggressive chemotherapy
 - Myocardial dysfunction
 - Extravasation of chemotherapeutic agent
 - Pancreatitis
 - Hemorrhagic cystitis
 - Cerebrovascular accident.

Box 33.10 lists the common oncologic emergencies.

Treatment

Timely diagnosis and appropriate treatment of these oncological emergencies can go a long way in reducing the morbidity and mortality.

FEBRILE NEUTROPENIA

Definition

The term refers to an absolute neutrophil count <500 cells/ mm^3 or <1000 cells/ mm^3 with an anticipated further fall in count to 500 cells/ mm^3 . Fever is defined as a single oral temperature of 38°C (100.4°F) or more. Less the count, more is the risk of infection. More prolonged the count, higher is the risk of infection.

Etiology

It may be secondary to oncological condition per se or an adverse drug reaction (ADR) of cytotoxic chemotherapy

Box 33.10 Common oncological emergencies**Hematological**

- Massive bleed with shock
- Severe anemia
- DIC
- Hyperleucocytosis
- Febrile neutropenia
- NEC
- Myelosuppression.

Space-occupying

- SVCS/SMS
- Raised ICP
- Brain herniation
- Pericardial effusion/Cardiac tamponade
- Spinal cord compression
- Massive hepatosplenomegaly.

Metabolic

- SIADHS
- TLS
- Hypercalcemia.

Inflammatory

Neutropenic enterocolitis (typhilitis).

Abbreviations: DIC, disseminated intravascular coagulation; NEC, necrotizing enterocolitis; SVCS, superior vena cava syndrome; SMS, superior mediastinal syndrome; ICP, intracranial pressure; SIADHS, syndrome of inappropriate ADH secretion; TLS, Tumorlysis syndrome.

which causes mucosal insult to the alimentary tract, often the primary site for infection. Predominant pathogens are Gram-positive and Gram-negative bacteria, fungi and viruses.

Clinical Features

Manifestations include septic shock, pneumonia, typhilitis with acute abdomen, and DIC.

Treatment

Antimicrobials in the form of broad-spectrum antibiotics plus antifungal drugs.

TUMOR LYSIS SYNDROME**Definition**

Tumor lysis syndrome, an almost fatal condition, is defined as a group of metabolic abnormalities that can occur as a complication of cancer chemotherapy, most often in lymphomas and leukemia.

Etiology

It is usually seen in ALL and NHL (most often Burkitt lymphoma)

Clinical Features

- Hyperkalemia causing cardiac arrhythmias
- Hyperuricemia
- Hypocalcemia causing tetany
- Hyperphosphatemia
- Metastatic calcifications
- Acute kidney injury.

Treatment

In addition to rehydration and alkalization, therapy revolves around allopurinol and rasburicase in case uric acid exceeds 10 mg/dL. In case of acute kidney injury, dialysis is indicated.

RAISED INTRACRANIAL PRESSURE**Etiology**

It results from brain edema from the primary malignancy.

Clinical Features

Headache, vomiting, bradycardia, hypertension, seizures, and cranial nerve palsies.

Treatment

Dexamethasone, antiepileptic drug (AEDs) and surgical decompression.

SUPERIOR VENA CAVA/MEDIASTINAL SYNDROME

This is the most common among the cardiothoracic emergencies.

Etiology

NHL, HL, ALL, germ-cell tumor, sarcomas.

Clinical Features

- Dyspnea, cough, dysphagia, hoarseness, headache, confusion and syncope
- Cyanosis and edema of face and upper part of the body.
- Pleural and/or pericardial effusion
- Aggravation of manifestations in supine position or when head is flexed (say for LP).

Diagnosis

Imaging studies (CXR, CT scan, echocardiogram).

Treatment

Irradiation, preferably over trachea only as a safeguard against development of irradiation-induced edema of small airways and respiratory distress. For edema, IV prednisolone (1 mg/kg/dose 6 hourly) is recommended.

HYPERLEUKOCYTOSIS**Definition**

Hyperleukocytosis is defined as a leukocyte count $>100,000/\text{mm}^3$. It occurs in leukemias.

Clinical Features

Manifestations include thrombosis causing stroke, hemorrhage, hypoxia and pulmonary infiltrates, etc.

Treatment

Treatment revolves around ensuring fluid and electrolyte balance, hydroxyurea, leukopheresis and chemotherapy.

SPINAL CORD COMPRESSION SYNDROME

Etiology

Spinal cord compression as a result of lymphoma, neuroblastoma, Ewing sarcoma, etc.

Clinical Features

Paraplegia, deep tendon reflexes, sluggish or lost, and hypotonia.

Treatment

- Dexamethasone
- Some cases may need surgical intervention.

BONE MARROW TRANSPLANTATION

(Hematopoietic Stem Cell Transplantation)

This is the only available curative treatment for leukemias, lymphomas, myelodysplastic syndromes, neuroblastoma, Wilms' tumor, retinoblastoma, brain gliomas and Ewing sarcoma.

Hematopoietic stem cell transplantation (HSCT) is transplantation of hematopoietic progenitor cells from bone marrow, peripheral blood or umbilical cord in order to reconstitute the bone marrow. When the cells are taken from the same individual, it is called **autologous**. when the donor is another individual, it is termed **allogeneic**. The donor may be a human leucocyte antigen (HLA)-matched sibling or an unrelated individual.

HSCT may prove life-saving for a number of malignant and non-malignant tumors that are otherwise fatal in due course of time. Bone marrow, umbilical cord blood and cytokine-mobilized peripheral blood are the currently employed sources of stem cells.

Indications

This new therapeutic modality, now available in India, may be indicated in several situations, provided that alternative therapeutic modalities are not able to offer reasonable chance for a cure or prolongation of survival (Box 33.11).

Procedure

An essential prerequisite is that the recipient must receive conditioning pretransplant immunosuppression with cyclophosphamide and low dose total body radiation to cut down risk of graft rejection or Graft versus host disease (GVHD).

Bone marrow is obtained from multiple sites on the posterior iliac crest, using sterile technique, under general anesthesia. Just 200 mL is enough in children. It is filtered to obtain a single cell suspension and to remove particles

that can possibly embolize to the lungs. The suspension is transfused IV to the recipient.

Hyperalimentation (parenteral) is advisable during the first month after transplant to prevent malnutrition and to improve survival. During this period, transplant patient frequently develops anorexia, nausea, vomiting and other symptoms related to GIT as a result of chemotherapy, radiation and GVDH. He/she is particularly vulnerable to develop infection and bleeding during this period of severe bone marrow aplasia. Effective supportive measures are, therefore, mandatory.

Complications

The complications of the procedure include:

- Graft rejection
- GVHD
- Infections (e.g. interstitial pneumonia)
- Recurrence of leukemia in ALL.

Outcome

It depends on:

- Stage of the disease at the time of transplantation
- Cytogenic abnormalities
- Technique of HLA matching
- Detection of superimposed infections and their therapy.

Box 33.11 Indications for bone marrow transplantation

Hematological malignancies

- Leukemias
 - Acute myeloid leukemia
 - Acute lymphoblastic leukemia
 - Chronic myeloid leukemia.

Nonhematological malignancies

- Lymphomas
 - Hodgkin lymphoma
 - Non-Hodgkin lymphoma
- Myelodysplastic syndromes
- Solid tumors
 - Neuroblastoma
 - Retinoblastoma
 - Brain tumors—gliomas
 - Ewing sarcoma.

Nonmalignant hematological disorders

- Aplastic anemia
- Fanconi anemia
- Hemoglobinopathies
 - Thalassemia major
 - Sickle-cell anemia.

Miscellaneous

- Immunodeficiency syndromes
- Inborn errors of metabolism.

Multiple Choice Questions

- Spot the wrong entry:
 - Childhood malignancies, though more aggressive, are usually responsive to chemotherapy
 - Leukemias top the list of childhood malignancies
 - Medulloblastoma is the most common malignancy of brain in childhood
 - Histiocytosis is rare in children
- All of the following entries about acute lymphoblastic leukemia (ALL) are correct, except:
 - Therapy and outcome is dictated by the genetic abnormalities in the leukemic clone
 - It is a great mimicker
 - Induction therapy is usually for 3 months
 - Notwithstanding best of therapy, relapse rate may be upto 30%
- All of the following entries about Non-Hodgkin lymphoma are correct, except:
 - Usually occurs in first decade of life
 - Extranodal disease is more common in childhood
 - Diagnosis is based primarily on histology
 - Modern chemotherapy is highly effective
- All of the following entries about retinoblastoma are correct, except:
 - Most common presentation is white pupillary reflex (leukocoria)
 - The gene is encoded on chromosome 13q14
 - Always sporadic
 - Second malignancy is frequent
- Each of the following is incorrect about childhood malignancies, except:
 - Febrile neutropenia requires therapy with broadspectrum antibiotics plus antifungal agents
 - Hodgkin lymphoma is an important cause of superior vena cava syndrome
 - Most cases of osteogenic sarcoma occur during adolescence
 - Most cases of Wilms' tumor need immediate surgical resection

Answers

1. C 2. D 3. A 4. C 5. B

Clinical Problem-solving

Review 1

A well-built 10-year-old presents with low-grade fever, moderate anemia, progressive weakness, easy fatigability and weight loss of 2–3 months duration. There is a massive splenomegaly (grade 5) with enlargement of liver (span 11 cm) and generalized lymphadenopathy. No evidence of portal hypertension. Antimalarial therapy given twice has no beneficial effect.

- Your clinical diagnosis.
- How to confirm the diagnosis?
- Any relationship with Philadelphia chromosome?

Review 2

A 2 ½ -year-old toddler, a known case of hemihypertrophy presents with a hard, fixed intra-abdominal large mass that does not cross the middle line. The mother claims having felt it only recently.

- What is the most likely diagnosis?
- How to confirm the diagnosis?
- Is there any connection between your diagnosis and child's hemihypertrophy?
- What is its prognosis?

Answers

Review 1

- Chronic myeloid leukemia.
- Bone marrow showing blast cells.
- Philadelphia chromosome (involving a reciprocal translocation between long arms of chromosomes 2 and 9) is encountered in as high as 90% cases of CML.

contd...

Review 2

1. The clinical picture is eminently in keeping with the diagnosis of Wilms' tumor (nephroblastoma).
2. A plain X-ray of abdomen showing a large soft tissue swelling displacing the gut supports the diagnosis. An IVP or ultrasonography showing dilatation of the renal calyces confirms the diagnosis.
3. Yes, hemihypertrophy is one the predisposing congenital conditions for Wilms' tumor. Other such conditions are Beckwith syndrome, aniridia, duplication of kidney or ureter, hypospadias, undescended testis, and ambiguous genitalia.
4. With aggressive therapy, 2-year disease-free survival rate is around 75–90%.

FURTHER READING

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IMMUNITY IN A NUTSHELL

Conventionally speaking, the term, **immunity**, refers to the defense mechanism that protects an individual against invasion by an infection. Today, it is believed to have extended defense function in the form of immunological surveillance limiting the development of tumor cells, malignant cell clones, molds and grafts. As shown in Figure 34.1, immunity may be innate or adaptive (acquired).

Innate immunity may be genetically passed on from one generation to another without depending on previous contact with a microbe. When it indicates a degree of resistance to all infections, it is termed **nonspecific**. When there is a resistance to a particular pathogen, it is called **specific**. Innate immunity is also expressed in relation to species, race or individual. Factors such as age, hormonal influences and nutrition considerably affect immune response. It should be considered primitive with no memory. Yet, it is the first line of defense against infections.

Adaptive (acquired) immunity, on the other hand, is highly evolved, quite specific and has memory. Exposure to a microbe second time provokes the adaptive immunity to recall previous express and react with a rapid rise in immune response.

IMMUNOLOGICAL SYSTEM: FUNDAMENTALS

Immunologic system operates with involvement of lymphocytes, plasma cells and macrophages (Fig. 34.2).

Cellular Components

Thymus and bursa of Fabricius (marrow in man) form the **central lymphoid tissues**. Spleen and lymph glands constitute the **peripheral lymphoid tissues**. Immunologic response has two stages:

1. Phagocytic
2. Lymphocytic

Phagocytic response consists of destroying the foreign agents (Fig. 34.3). The key cells involved in this response are

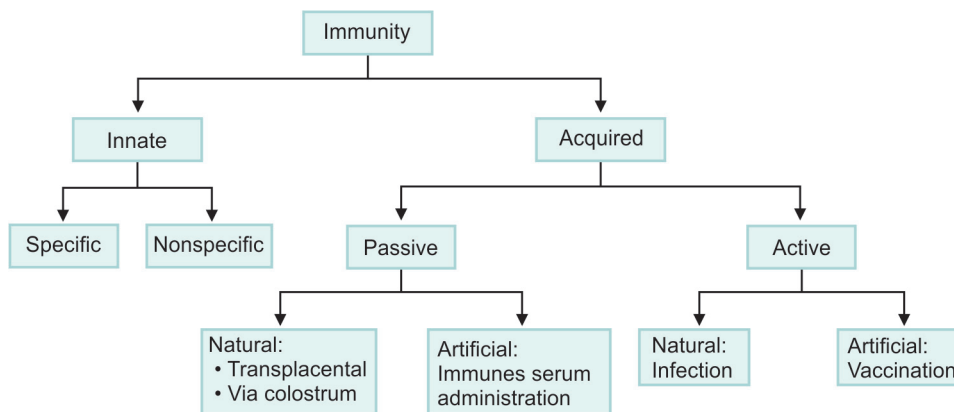


Fig. 34.1: Immunity. Classification and subclassification.

CELLS	Leukocytes				Other
	Lymphocytes			Auxillary cells	
	B cell	T cell	Large	Mononuclear Neutrophil Eosinophil Basophil Mast cell Platelets	Tissue cell
Soluble mediators	Antibodies	Cytokines	Complement	Inflammatory mediators	Interferon, cytokines

Fig. 34.2: Cells of the immune system.

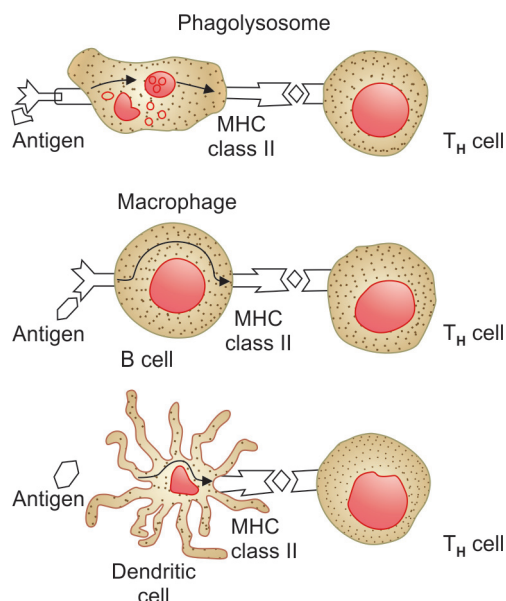


Fig. 34.3: Antigen presenting cells.

Abbreviations: MHC, major histocompatibility complex; T_H cell, T helper cells.

neutrophils from the circulating blood and macrophages from the reticuloendothelial system, particularly the lymph glands and the spleen.

In the conduct of phagocytic response, additional factors such as complement and opsonin may be required. If the invading agent is destroyed by phagocytosis, immune response stops here only. However, if antigenic products are produced, the next step, i.e. lymphocytic response, which is the sheet-anchor of the immunologic system, must follow.

Complement System

Complement refers to a series of factors in the normal serum that are activated by antigen-antibody interaction and subsequently mediate a number of biologically significant consequences. It forms about 10% of human serum globulin. There are 9 distinct components of complement system, one of them having 3 subunits ($C'1g'$, $C'1r'$, $C'1s'$) thereby making a total of 11 proteins. Chain of event in which complement components react in specific sequence following activation of antigen-antibody complexes and culminating in immune cytolysis is known as **classical C' pathway**. Activation of $C'3'$ without prior participation of $C'1'$, $C'4'$ and $C'2'$ is called **alternate pathway**. Activities of the complement immunity against infection may be outlined as under:

- **$C'1'$ and $C'4'$, $C'1'$, $C'4'$, $C'2'$ and $C'3'$:** Neutralization of viruses
- **$C'4a'$, $C'3a'$, $C'5a'$:** Capillary dilatation
- **$C'5a'$:** Chemotaxis of neutrophils, monocytes, eosinophils
- **$C'3b'$:** Opsonization, enhancement of cell-mediated cytotoxicity stimulation of production of B cells lymphokines
- **$C'3b'$, $C'3d'$:** Increased induction of antibody formation
- **$C'3c'$:** Induction of granulocytosis
- **$C'5'$:** Opsonization of fungi

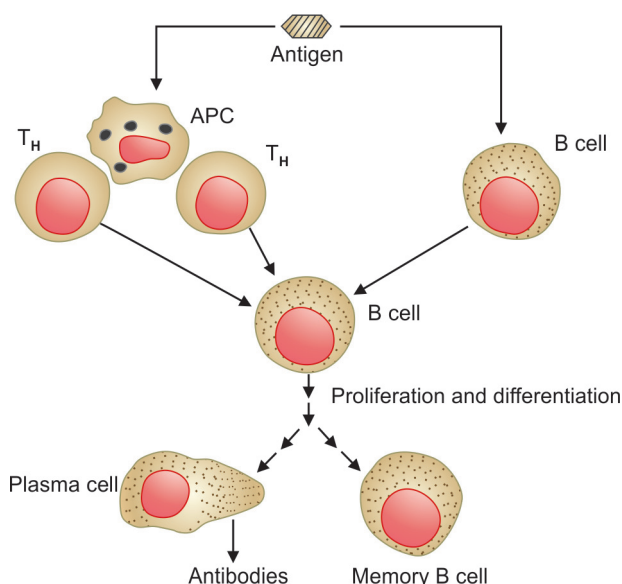


Fig. 34.4: B cell activation and antibody formation.

Abbreviations: APC, antigen presenting cells; T_H , T helper cells.

- **$C'1'-C'6'$:** Inactivation of endotoxin
- **$C'1'-C'9'$:** Lysis of viruses, virus-infected cells, tumor cells, mycoplasma, protozoa, spirochetes and bacteria. Lymphocytic response is affected by either humoral or cellular mechanism, or both.

Humoral immunity is concerned with synthesis and release of antibodies (immunoglobulins) secreted by plasma cells, as also complement, interferon and lysozyme. Its functional cell is B lymphocyte, the bursa-dependent cell, which stems from the precursor in the bone marrow.

About 25% lymphocytes are B cells. They are mostly restricted to lymphoid tissue. T helper cells are essential for their transformation into antigen recognition cells and production of immunoglobulins. T suppressor cells suppress the activity and lessen formation of antibodies. Thus, the immune response is maintained within a tolerable level.

On entry of an offending agent (antigen), B cells develop into plasma cells which secrete specific antibodies to antagonize the antigen. Once the illness is over, level of circulating antibodies falls slowly over a period of several weeks. In case the same illness returns, level of antibodies against the antigen rises rapidly, thereby halting the invasion by the same antigen and acquisition of specific immunity. This happens since the body remembers the mechanisms by which the antibody was produced earlier. This is called **immunologic memory** (Fig. 34.4). Functions of the B cells include:

- Protection against *Staphylococcus*, *Streptococcus*, *Hemophilus*, *Pneumococcus*
- Neutralization of viruses to prevent initial infection
- Action as a barrier along gastrointestinal and respiratory tracts
- Active lysis of cells of autologous origin or engagement in antigen-antibody complex disease
- Interference with T killer cells activity, or directly or indirectly blocking the reaction.

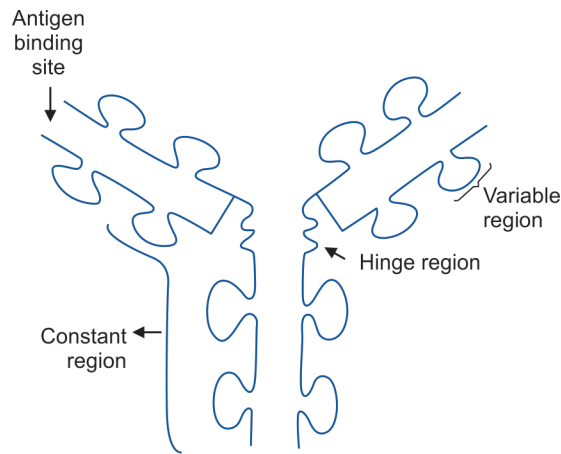


Fig. 34.5: Structure of immunoglobulin.

IMMUNOGLOBULINS

Immunoglobulins (Figs 34.5 and 34.6) are the globulin molecules associated with antibody activity, extending in electrophoretic activity from alpha to gamma regions. Basically their structure consists of two polypeptide chains. **First, i.e.** light chain, may be kappa (κ) or lambda (λ). **Second, i.e.** heavy chain, imparts class specificity. Structurally, 5 major types are recognized at present—(1) IgG, (2) IgA, (3) IgM, (4) IgD and (5) IgE.

IgG is the major immunoglobulin, constituting around 75% of the immunoglobulin content of the serum. In the fetus, it is by far the only immunoglobulin present. The newborn receives it, by transport across the placenta, in sufficient amount depending on the gestational age, weight and efficiency of placental function. IgG so received from the mother gradually begins to fall after birth so that at 2–6 months the infant suffers from what is known as physiological hypogammaglobulinemia G which is discussed later in this very Chapter. There are further subclasses of IgG, say IgG1, IgG2, IgG3 and IgG4, based on differences in heavy polypeptide chain (Fc).

IgA and IgM are very low at birth, the adult levels reaching by the age of 2 years. The exact role of IgM in immune response is not yet clearly understood. IgA is, however, well known to play an important part in human

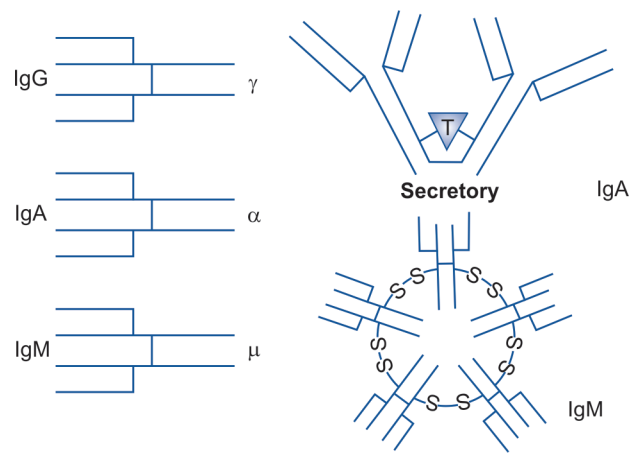


Fig. 34.6: Structure of IgG, IgA and IgM.

defense against infection, particularly pertaining to respiratory tract and gastrointestinal tract (GIT). Agammaglobulinemia is always accompanied by deficiency of secretory component of IgA (Table 34.1).

Cell mediated immunity (CMI) is affected by its functional cell, T lymphocyte, which is thymus-dependent and initially stems from the precursors in the bone marrow as is the case with B lymphocytes. These cells form about 75% of the lymphocytes and mostly circulate in blood, interstitial space and lymph in the marrow. A recently described thymus hormone, **thymosin**, is claimed to maintain their activity. Functions of T lymphocytes include:

- T helper function
- T suppressor function
- T killer function
 - Containment of acid-fast bacilli
 - Containment of certain viral infections (Epstein-Barr virus {EBV}, slow virus)
 - Containment of fungal infections (*candida*)
 - Containment of protozoal infections (*Pneumocystis carinii*)
 - Rejection of allograft (tumors)
 - Graft vs host disease (GVHD)
 - Contact dermatitis.

Table 34.1: Properties of immunoglobulins

Properties	IgG	IgA		IgM	IgD	IgE
		Serum	Secretory			
Molecular weight	140,000	160,000	370,000	900,000	160,000	2000,000
Placental transfer	Yes	No	No	No	No	No
Complement fixation	Yes	No	Yes	Yes	No	No
Polymer formation	No	No	Yes	Yes	No	Doubtful
Blocking antibody	Yes	Doubtful	Yes	Doubtful	Doubtful	Doubtful
Secreted by mucus surfaces	Weak	Weak	Yes	Weak	No	Yes
Fixation to mast cell	No	No	No	No	No	Yes
Fixation to macrophages	Yes	No	No	No	No	No
Bactericidal function	Yes	No	No	Yes	No	No
Role	Protection of tissue fluid	Protection of circulation	Protection of mucosal surface	Protection of circulation	Unknown	Reaginic activity

Lymphokines are soluble mediator substances which are liberated when an antigen-sensitive T lymphocyte comes into contact with the specific antigen at the periphery. The major soluble factors include:

- Mitogenic factor which enhances lymphocyte multiplication
- Permeability increasing factor
- Lymphocytotoxin
- Migration inhibiting factor which favors phagocytosis
- Transfer factor which transfers to the uncommitted cells the characteristics of the antigen-sensitized cells.

Cellular immune response ends up in destruction of the antigen. This may either be directly through the action of the sensitized lymphocytes or by activity of lymphocytotoxins.

IMMUNODEFICIENCY STATES

By immunodeficiency is meant that one or more defense mechanisms are impaired or lacking. It may be **primary** when there is no obvious systemic disease to explain its occurrence. In the **secondary type**, the cause is clearly outside the lymphoid system, e.g. protein energy malnutrition, malignancy, infections, drugs, etc. The immune mechanism is affected either as a part of generalized disease process or due to influence of certain aspect of the primary disease involving the lymphoid system. Primary deficiency is far less than the secondary deficiency (Fig. 34.7). Box 34.1 lists various modes of presentation of immunodeficiency.

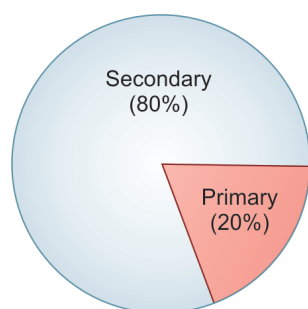


Fig. 34.7: Relative frequency of primary and secondary immunodeficiency.

Box 34.1 Modes of presentation of immunodeficiency

- Recurrent infections—*Pneumocystis carinii*, *Aspergillus fumigatus*, SSPE
- GIT upset in the form of unexplained protracted diarrhea/malabsorption, recurrent infestation with *L. giardia*
- Recurrent eczema without any obvious cause
- Failure to thrive which is difficult to explain
- Unusual vaccination reactions, e.g., infection after BCG
- Autoimmune disorders, e.g. rheumatoid arthritis
- Malignancy, e.g. leukemia
- Disorders of parathyroids and thymus associated with developmental anomalies of face, e.g. hypocalcemic tetany
- Ataxia telangiectasia, characterized by hereditary cerebellar ataxia and conjunctival telangiectasia together with frequent sinopulmonary infections
- Hereditary angioneurotic edema
- Nutritional deficiency state, e.g. protein energy malnutrition, iron deficiency anemia.

Abbreviations: SSPE, subacute sclerosing panencephalitis; GIT, gastrointestinal tract; BGG, Bacillus Calmette Guérin.

Box 34.2 Classification of primary immunodeficiency

B cell (humoral) defects

- Physiologic hypogammaglobulinemia G
- Transient hypogammaglobulinemia G
- Panhypogammaglobulinemia (congenital agammaglobulinemia, Bruton disease)
- Dysgammaglobulinemia (common varied immunodeficiency)
 - Selective IgA deficiency
 - Selective secretory IgA deficiency
 - Selective IgM deficiency
 - IgG subgroup deficiency.

T cell (cellular) defects

- Congenital thymic hypoplasia (DiGeorge syndrome)
- Nezelof syndrome
- Cartilage-hair hypoplasia (CHH) syndrome.

Combined B and T cell defects

- Wiskott-Aldrich syndrome
- Ataxia telangiectasia.

Neutrophil defects

- Qualitative
 - Chronic granulomatous disease
 - Chediak-Higashi syndrome
 - Job syndrome
 - Myeloperoxidase deficiency
 - Lazy leucocyte syndrome.
- Quantitative
 - Congenital chronic neutropenia
 - Isoimmune neonatal neutropenia
 - Cyclic neutropenia
 - Shwachman-Diamond syndrome
 - Congenital splenic defects.

Complement defects

- Hereditary angioneurotic edema.

PRIMARY IMMUNODEFICIENCY STATES

Box 34.2 gives classification of primary immunodeficiency.

B CELL DEFECTS

Clinical manifestations of B cell (humoral immunity) defects include recurrent bacterial pneumonia, sepsis, septicemia, meningitis and nodular lymphoid hyperplasia.

- **Physiological hypogammaglobulinemia G** is a self-limiting condition, occurring at 3–6 months of age when the maternal IgG is depleted and yet the infant has not been able to synthesize enough IgG to make up for the loss. Infants of low birth weight (LBW) suffer from this state more frequently. Usually, it causes no serious problem.
- **Transient hypogammaglobulinemia G** is an extension of the physiologic deficiency state to as much as 1–4 years when the normal immunoglobulin levels may be attained. It results from gross delay in synthesis of immunoglobulins. Serum IgG level may be under 200 mg/dL. Both sexes are affected, the incidence being higher in preterm infants. The condition is associated with frequent bacterial infections in which situation the infant needs to be administered 0.7 ml/kg intramuscularly (IM) of immune globulin every 2–4 weeks for about 6 months.
- **Panhypogammaglobulinemia (congenital agammaglobulinemia, Bruton disease)**, usually X-linked, is char-

acterized by low levels of all the three major immunoglobulins and almost total absence of antibody response. Clinical manifestations include repeated infections with *Pneumococcus*, *staphylococcus* and *Hemophilus influenza* as also viruses, especially echotype 30, skin disorders like eczema and recurrent abscesses, malabsorption, *Lamblia giardia* infestation, disaccharide intolerance and increased incidence of malignancy. Diagnosis is made by assaying the serum immunoglobulin IgM and IgA nearly absent and IgG invariably less than 200 mg/dL. Treatment consists of giving a loading dose of 1.4 ml/kg followed by 0.7 mL/kg of immune serum globulin every 4 weeks, or plasma. Daily prophylaxis with cotrimoxazole is advocated by some authorities. Long-term complications include bronchiectasis, rheumatoid arthritis, malignancy, hemolytic anemia and infection with *Pneumocystis carinii*.

- **Dysgammaglobulinemia (common varied immunodeficiency)** refers to states of absence or deficiency of one or more immunoglobulins. There may well be a compensatory rise in other immunoglobulins.

In **selective IgA deficiency**, recurrent respiratory infections and chronic diarrhea are the common manifestations. There is a remarkable association with autoimmune disease like systemic lupus erythematosus (SLE) and rheumatoid arthritis and allergic disorders like asthma and eczema. Administration of diphenylhydantoin sodium may also produce this immunologic state. Serum IgA level is under 5 mg/dL. The patient, however, has normal capacity to synthesize IgG and IgM antibodies. Other functions of immunity are normal. The condition may be transient or persistent. It is the most common primary immune deficiency, forming around 20% of the group. Overall incidence varies between 1 in 400 and 1 in 1,000.

Selective deficiency of secretory IgA may occur in two situations—(1) sudden infant death syndrome (SIDS) and (2) chronic diarrhea.

In **selective IgM deficiency**, prominent clinical features include fulminant hematogenous spread of bacterial infections, atopy and splenomegaly. Common associates are Whipple disease, regional enteritis and lymphoid nodular hyperplasia. A vigorous antibiotic treatment as soon as infection is suspected is indicated.

In IgG subgroup deficiency, total IgG level remains normal. The heterogeneity of its electrophoretic mobility is, however, restricted. As a result antibody formation to some antigen is normal, but poor to others. Increased susceptibility to infections is its hallmark. Gammaglobulin therapy proves helpful in some cases.

T CELL DEFECTS

Clinical manifestations suggestive of T cell defects include:

- Systemic illness following vaccination with any live virus or Bacillus Calmette Guérin (BCG); unusual life-threatening complication following infection with ordinary benign viruses (e.g. giant cell pneumonia with measles, varicella pneumonia).
- Chronic oral candidiasis persisting after 6 months of age and resisting adequate chemotherapy.
- Chronic mucocutaneous candidiasis.

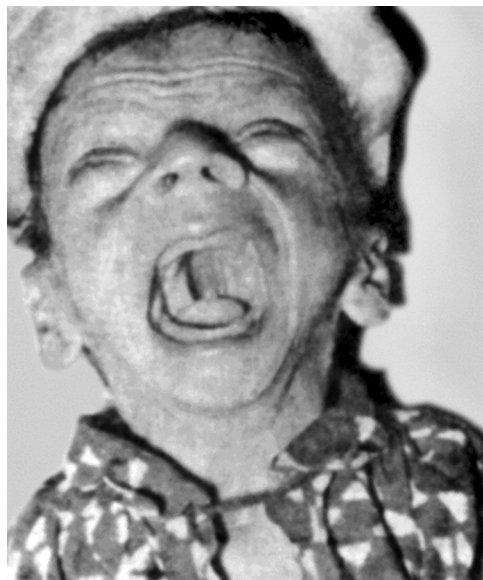


Fig. 34.8: DiGeorge syndrome. The subject presented with neonatal tetany (that responded to IV calcium, high doses of vitamin D), micrognathia, abnormal ears (both in shape and placement), high-arched and cleft palate, and right-sided aortic arch in CXR. There was demonstrable deficiency in T cell system with normal serum globulin levels. The infant succumbed to sepsis following recurrent infections, including resistant oral and anorectal thrush lingering on over a period of 3 months. Autopsy confirmed presence of only rudimentary thymus.

- Features (fine, thin hair, short-limbed dwarfism with characteristic roentgenographic features) of cartilage-hair hypoplasia (CHH) syndrome.
- Intrauterine GVHD disease. Most characteristic feature is scaling erythroderma and total alopecia (absence of eyebrows quite striking).
- Graft-vs-host disease after blood transfusion.
- Hypocalcemia in newborn (DiGeorge syndrome).
- Small (<10 μm diameter) lymphocytes, count persistently under 1500/mm³.

Congenital thymic hypoplasia or aplasia (DiGeorge syndrome) is characterized by embryonic combined deficiency of thymus and parathyroids (both arise from third and fourth pharyngeal pouches) in association with congenital defects of heart and aortic arch (usually stenosis), hypoplastic mandible, defective ears and short philtrum (Fig. 34.8). Hypocalcemic tetany in the early neonatal period may be the first presenting feature. It responds to high doses of calcium intravenous (IV) and vitamin D, provided that low intake of phosphorus is ensured. Eventually, the patient may undergo spontaneous cure or may need thymic transplantation.

Nezelof syndrome is characterized by the picture seen in DiGeorge syndrome minus parathyroid or cardiac involvement. **Cartilage-hair hypoplasia syndrome** is characterized by short-limbed dwarfism, scanty hair (with missing central pigmented core) and neutropenia.

COMBINED B AND T CELL DEFECTS (Combined Immunodeficiency)

Clinical symptoms suggestive of combined B and T cell defects include:



Fig. 34.9: Wiskott-Aldrich syndrome. Besides extensive skin lesions that showed waxing and waning from early infancy, this 1-year-old had recurrent epistaxis and purpura, discharging ears and frequent intercurrent infections. Platelet count was $40,000/\text{mm}^3$ and TLC $8,000/\text{mm}^3$ with only 23% lymphocytes. Level of IgM was remarkably low though IgA and IgG levels were elevated.

- Features of all above, except chronic mucocutaneous candidiasis and nodular lymphoid hyperplasia
- Features of Wiskott-Aldrich syndrome
- Features of ataxia telangiectasia.
 - **Wiskott-Aldrich syndrome (WAS)**, an X-linked recessive disorder, is characterized by eczema, thrombocytopenic purpura, discharging ears and susceptibility to infection (Fig. 34.9). Predominant IgM deficiency is remarkable. There is, thus, inability to form antibodies to carbohydrate antigens. Mild dysfunction of T cell occurs. Terminally, patients frequently develop malignant reticuloendotheliosis.
 - **Ataxia telangiectasia**, an autosomal recessive disorder, is characterized by cerebellar ataxia, ocular and cutaneous telangiectasia, chronic sinopulmonary disease and endocrinal abnormalities. IgA and IgE deficiency and variable degree of T cell deficiency constitute its hallmark. Death usually follows development of malignant lymphoma.

NEUTROPHILS DEFECTS

Chronic granulomatous disease (CGD) is characterized by granulomatous lesions in skin, lymph nodes, liver, lungs, spleen and bones (Fig. 34.10). Infection occurs usually by bacteria which are normally of low virulence and fungi. Cellular and antibody responses are normal. The real defect lies in the bactericidal activity of the neutrophils due to failure to generate microbial oxygen products. The defect can be detected *in vitro* by the nitroblue tetrazolium (NBT) test. Normally, almost 90% of leucocytes reduce the dye to a purple-black compound. In granulomatous disease, hardly 10% or even less are able to do so. The disease is usually X-linked recessive (males affected,



Fig. 34.10: Chronic granulomatous disease. This 10-year-old boy presented with chronic generalized lymphadenopathy (most marked in the cervical and axillary regions where the nodes showed multiple discharging sinuses), hepatosplenomegaly, and remarkable bilateral hilar prominence as also widening of the superior mediastinum (not due to thymus) in the chest X-rays. Investigations revealed no convincing evidence of tuberculosis. Empirically, antituberculous therapy was given without any relief. Later, nitroblue tetrazolium test (NBT) test showed that only 7% of leucocytes reduced the dye to purple-black. Cellular and antibody responses were found to be normal.

females carriers). Long-term prophylactic therapy with cotrimoxazole is of considerable value.

- **Chédiak-Higashi syndrome (CHS)**, an autosomal recessive disorder, is characterized by partial albinism and recurrent pyogenic infections (especially of skin). Giant cytoplasmic granules in leucocytes are characteristics. The bactericidal defect seems to be due to change in lysosome membrane. Response to corticosteroids is often gratifying.
- **Job syndrome (hyper-IgE syndrome)**, a condition quite similar to chronic granulomatous disease, is characterized by recurrent cold abscesses (staphylococcal), skin pigmentation, chronic eczema and red hair. It occurs exclusively in males. IgE levels are remarkably high. Many patients have depressed chemotaxis of neutrophils and monocytes. The underlying defect appears to be in CMI.
- **Myeloperoxidase deficiency** is characterized by susceptibility to *Candida* septicemia since the defect causes inability to kill fungi, especially *Candida*.
- **Lazy leucocyte syndrome**, a specific disorder of leucocyte function, is characterized by gingival stomatitis, recurrent upper respiratory infection (URI), including otitis, skin infection and persistent fever. There is leukopenia and absence of polymorphonuclear motility from bone marrow into circulation.

Congenital chronic neutropenia, isoimmune neonatal neutropenia, cyclic neutropenia, Shwachmann-Diamond syndrome and congenital splenic defects figure among the prominent quantitative deficiency states of neutrophils.

Box 34.3 Warning signs of primary immunodeficiency

- Four or more infections in a year
- Two or more attacks of pneumonia in a year
- Two or more months of antibiotics with poor outcome
- Failure to thrive
- Recurrent deep skin infections or organ abscesses
- Persistent oral thrush or candida abscess beyond infancy
- Need for IV antibiotics for clearing infections
- Two or more deep-seated infections such as cellulitis or meningitis
- Family history of immunodeficiency.

COMPLEMENT DEFECTS

Deficiencies of individual fractions of complement are very rare. Absence of C'1 may cause **hereditary angioneurotic edema** characterized by swelling of the affected part. With involvement of gut wall, severe abdominal cramps may lead to unnecessary surgery. Laryngeal edema may prove fatal. SLE may occur as a complication. Hypercatabolism of C'3 causes increased frequency of infections and that of C'5 causes recurrent pyogenic infections.

RED FLAG SIGNS FOR PRIMARY IMMUNODEFICIENCY

Primary immunodeficiency, though much less frequent than secondary immunodeficiency, should be suspected in certain situations (Box 34.3).

SECONDARY IMMUNODEFICIENCY

An overwhelming majority of immunodeficiency states are secondary to other defects (Table 34.2).

DIAGNOSTIC APPROACH IN IMMUNODEFICIENCY**Clinical Clues**

High index of suspicion is of vital importance in identifying children with immunodeficiency (Box 34.4).

In the birth history, it is desirable to find out history of rubella during pregnancy, as also about the baby's gestational age, birth weight and any neonatal illness. Any evidence of unusual or severe course of childhood diseases such as measles and chickenpox should be sought.

Physical examination of a suspected case is quite important. The child with immunodeficiency invariably shows growth retardation with short stature, irritability and pallor. Pyoderma, eczema, stomatitis, perianal excoriation and ear discharge are common accompaniments. Despite recurrent URI, tonsils are either rudimentary or absent and cervical lymph nodes are absent.

In Table 34.3 are summarized the clinical clues on physical examination and the likely immunodeficiency state. Table 34.4 lists the skin lesions and the related immune defects.

Investigations

- Initial/screening tests
 - Complete blood picture TLC/DLC: A total count of less than 2,000/mm³ suggests T cell deficiency.

Table 34.2: Classification of secondary immunodeficiency**B cell (humoral) defects**

- Loss of immunologic material, e.g. nephrotic syndrome, protein-losing enteropathy
- Infections, e.g. malaria, EBV infection, trypanosomiasis.

T cell (cellular) defects

- Nutritional deficiency state, e.g. severe protein energy malnutrition, iron, zinc, biotin, vitamin B, or folate deficiency
- Viral infections, e.g. HIV, measles, intrauterine infections
- Chronic granulomatous disease, e.g. tuberculosis, sarcoidosis, leprosy
- Renal failure
- Reticuloendotheliosis
- Thoracic duct fistula
- Intestinal lymphangiectasia
- Severe tricuspid regurgitation.

Combined B and T cell defects

- | | |
|-----------------------------|------------------------------|
| • ADA deficiency | • Irradiation |
| • NP deficiency | • Bone marrow aplasia |
| • Immunosuppressive therapy | • Severe/fulminant infection |
| • Cytotoxic therapy | • Congenital rubella |

Neutrophil defects

- | | |
|--------------------------------|--------------------------|
| • Malnutrition | • Kartagener syndrome |
| • Myeloid leukemia | • Ichthyosis |
| • Down syndrome | • SLE |
| • Acrodermatitis enteropathica | • Rheumatoid arthritis |
| • Cryoglobulinemia | • Hodgkin lymphoma |
| • Viral infection | • Overwhelming infection |

Complement defects

- | | |
|-------------------------------------------|----------------------------------|
| • Chronic membranoproliferative nephritis | • Thalassemia |
| • SLE | • Splenectomy |
| • Neonatal period | • Nephrotic syndrome |
| • Severe burns | • Lepromatous leprosy |
| • Malnutrition | • Bacterial endocarditis |
| • Anorexia nervosa | • Malaria |
| • Leukemia on drugs | • Glandular fever, Reye syndrome |
| • Chronic cirrhosis | • Gram-negative septicemia |
| | • Sickle cell disease |

Abbreviations: ADA, adenosine deaminase; NP, nucleoside phosphorylase; EBV, Epstein-Barr virus; SLE, systemic lupus erythematosus HIV, human immunodeficiency virus.

Box 34.4 Clinical clues (in history) raising suspicion of immunodeficiency

- The most common reason for suspecting immunodeficiency is very high frequency of severe infections. Remaining characteristics of infections such are:
 - Prolonged duration with complications
 - Repeated infections with hardly any symptom free period
 - Multisystem involvement
 - Invasion with unusual micro-organisms.
- Adverse reactions to live vaccines should also arouse suspicion of an immunodeficiency state.
- Children with asthma or other allergic diseases have some 7% chances of suffering from an immunodeficient disorder.
- Chronic diarrhea defying diagnosis/poor response to therapy may be a manifestation of an immunodeficient state. Such a child suffers from persistent giardiasis and failure to thrive.
- Family history of a severe infection, early deaths of members, collagenosis or consanguinity may provide a clue to an inherited immunodeficiency defect. It is a good idea to prepare a pedigree tree.
- Past history should also include history of surgery on tonsils and adenoids, radiation to thymus and human gammaglobulin therapy.

Table 34.3: Clinical clues (on physical checkup) raising suspicion of immunodeficiency states

Clues	Likely immunodeficiencies
Growth retardation, ill look, pallor, irritability	Common to most immunodeficiencies
Peculiar faces (micrognathia, hypertelorism, low-set ears, notched pinna)	DiGeorge syndrome (congenital thymic hypoplasia)
Albinism	Chediak-Higashi disease
Red hair	Job syndrome
Fine hair	Cartilage hair hypoplasia with SCID
Alopecia	SCID
Conjunctivitis	IgA deficiency
Uveitis	IgA deficiency
Telangiectasia	Ataxia telangiectasia
Oral thrush with ulcers	Chronic mucocutaneous candidiasis
Macroglossia	CMI immunodeficiency
Chronic ear discharge	Chronic granulomatous disease, X-linked lymphoproliferative disease, Wiskott-Aldrich syndrome, opsonic function disturbance, immunoglobulin deficiency
Excoriation of nasal mucosa and sinusitis	IgA deficiency
Bronchiectasis/pneumonia	Immunoglobulin deficiency
Congenital heart disease	CMI immunodeficiency
Dextrocardia	Immotile cilia syndrome
Hepatosplenomegaly	Chronic granulomatous disease
Ataxia	Ataxia telangiectasia
Arthritis	Complement deficiency
Poor muscle mass with joint enlargement	IgA deficiency

Abbreviations: SCID, severe combined immunodeficiency; IgA, immunoglobulin; CMI, cell-mediated immunity.

Table 34.4: Characteristic skin manifestations in immunodeficiency

Skin findings	Associated immune defects
Eczema or petechiae	Wiskott-Aldrich syndrome
Telangiectasia	Ataxia-telangiectasia
Oculocutaneous albinism	Chédiak-Higashi syndrome
Dermatomyositis like rash	X-linked agammaglobulinemia
Chronic dermatitis	Hyper IgE syndrome
Lupus-like rash	Complement deficiency
Cutaneous scars and nonhealing ulcers	Phagocytic defects
Molluscum contagiosum	T cell defect
Extensive warts	T cell defect
Candidiasis	T cell defect

Howell-Jolly bodies point to impaired splenic function or absolute asplenia. Giant granules in granulocytes suggest Chediak-Higashi disease.

- HIV serology
- Chest-X ray
- Delayed skin test.

■ Specific tests

- **Immunoglobulin levels:** IgA, IgG and IgM are done initially and, if warranted, IgD and IgE may be done at a later stage. The values need to be compared with the normal values on age-matched controls.
- **Schick test:** This test is of significance in only subjects who have had diphtheria pertussis and tetanus (DPT) or DT vaccine. “No reaction” in these individuals means good immunological status.
- **Opsonin function:** The function of opsonins (the two chief ones are antibodies and complements) is tested by mixing white blood cells and bacteria in the presence of subject’s serum. After incubation at 37°C for 20 minutes, a stained preparation is prepared. It is examined for the number of bacteria which have been engulfed by the cells. A count of less than 300 bacteria/100 white cells suggests abnormal opsonic function.
- Hemagglutinin titer.
- Delayed hypersensitivity skin tests using Streptokinase-Streptodornase.
- NBT test.
- CH50 complement compound assay.
- Human leucocyte antigen (HLA) typing.
- Enzyme assays.

A good history, clinical examination and the screening tests mentioned here are capable of identifying about a large majority of the immunodeficiency states in pediatric practice.

Treatment

It is outlined in discussion of specific entities in appropriate chapters. Generally speaking, attention to the primary causative condition (in most cases PEM) is of key importance. Specific modalities include plasma infusion (complement deficiency), intravenous immunoglobulin (IVIG) (X-linked gammaglobulinemia, immune thrombocytopenic purpura {ITP}, Kawasaki disease, Guillain Barre syndrome {GBS}, hemolytic-uremic syndrome {HUS} etc.), interferon gamma (chronic granulomatous disease), zidovudine (acquired immunodeficiency syndrome {AIDS}), etc.

IMMUNOLOGIC BASIS OF AUTOIMMUNE DISEASES

That human body normally produces antibodies against a foreign substance and not against its own constituents (the so-called “self-antigen”), which the body readily recognizes, is well established. A breakdown in the mechanism of recognition of self-antigen and nonself-antigen may lead to development of autoantibodies in a group of disorders referred to as autoimmune diseases.

Box 34.5 Two groups of autoimmune diseases

- **Group I:** Associated with common body antigen
 - Rheumatoid arthritis
 - ITP
 - SLE
 - Scleroderma
 - Polyarteritis nodosa
 - Acquired hemolytic anemia.
- **Group II:** Associated with inaccessible antigen
 - Hashimoto disease
 - Sjögren syndrome
 - Sympathetic ophthalmitis
 - Multiple sclerosis
 - Peripheral neuritis.

Abbreviations: SLE, systemic lupus erythematosus; ITP, Immune/idiopathic thrombocytopenic purpura.

Types of Autoimmune Diseases

Two groups of autoimmune disease are:

1. Autoimmune diseases associated with common body antigen.
2. Autoimmune diseases associated with inaccessible antigen. Box 34.5 lists the diseases falling under the two groups.

Mechanism of Development

One of the following mechanisms may operate in the production of autoimmune disease:

- Body antigen may not be recognized as self-antigen, leading to production of autoantibodies.
- An infection or a drug may modify an endogenous molecule so that its antigenic determinants are changed and virtually a new antigen is formed, e.g. rheumatoid arthritis in which there is denaturation of gammaglobulin.
- Antibodies to a vaccine (say antirabies vaccine) may cross-react with some host components, e.g. antirabies vaccines.
- Constant exposure of lymphoid tissues to small amounts of antigens may lead to breakdown of immune tolerance (complete or partial) and production of forbidden clones, e.g. SLE. Here B cells are responsive but T cells are not.
- B cell stimulation may result from powerful adjuvant effect of microbes.

IMMUNOLOGIC BASIS OF ALLERGY (ATOPY)

Allergy is an altered state of hypersensitivity resulting from the interaction of antigen with humoral antibody or cellular immune response, occurring in a host sensitized by prior exposure to the antigen.

- **Type I reaction**, also called **immediate reaction**, refers to anaphylaxis, atopy etc. that appears rapidly and disappears rapidly. It is mediated by IgE (only to some extent by IgG) which has unique character of binding homologous mast cells and basophils. Contact with antigen stimulates cyclic adenosine monophosphate (CAMP) system and calcium transport across cell membrane, leading to release of histamine, SRS-A, serotonin, bradykinin and prostaglandins. Eventually manifestations such as bronchospasm and enhanced vascular permeability result.

- **Type II reaction** refers to cytotoxic response, e.g. thrombocytopenia, hemolytic anemias. IgG and IgM as also complement system participates in it.
- **Type III reaction** refers to immune complex or toxic complex, e.g. serum sickness, Arthus phenomenon. IgG, IgM and complement take part in it.
- **Type IV reaction**, also called **delayed reaction**, and is manifested by infiltration with mononuclear cells. T cells, lymphokines and macrophages are involved in this response.
- **Type V reaction** is antibody dependent, cell mediated cytotoxic reaction, brought about by nonimmune killer cells (macrophages or lymphocytes), e.g. thyroiditis.

IMMUNOLOGIC ASPECTS OF MALIGNANCY

Immunodeficiency in association with malignancy may be primary or secondary.

Examples of primary immunodeficiency with malignancy include Wiskott-Aldrich syndrome leading to lymphoid neoplasia and hypogammaglobulinemia causing thymoma. The possible reasons are:

- Failure of an immunologic rejection of normally occurring aberrant cells
- A tendency to develop abnormal lymphoid cells
- A continuous overstimulation by antigens of infecting agents
- Immunodeficiency leading to defects in dealing with an oncogenic virus.

Examples of malignancy occurring secondary to immunodeficiency disease include multiple myeloma and chronic lymphatic leukemia. Treatment with cytotoxic drugs and local irradiation—though desirable—may lead to gross hypertrophy of nonmalignant lymphoid tissue and damage to the limited immunity mechanism in such patients.

IMMUNODEFICIENCY AND SPECIAL RISKS

It is a sound policy not to administer live vaccines to patients with known immunodeficiency. In selected cases, one may consider giving the vaccine in a small dose combined with hyperimmune immunoglobulin.

Even in the case of killed vaccines, care needs to be exercised. Administration of TAB to immunodeficient individuals may result in HUS. Subject with cell mediated immunodeficiency should, as far as possible, not receive blood transfusion. In unavoidable circumstances, only irradiated blood should be given.

INTRAVENOUS IMMUNOGLOBULINS

The availability of IVIG for therapeutic use offers a relatively new avenue in pediatric therapy. IVIG is a pooled normal, intact polyspecific IgG. It is derived from the plasma of healthy human donors.

Composition

IVIG is a mixture of IgG (95%), IgM (2%) and IgA (1%). Further the dominant component (IgG) is a mixture of

Box 34.6 WHO prerequisites for IVIG preparation

- There should be no aggregation or fragmentation.
- Half-life should be same as in case of native IgG.
- Normal subclass distribution.
- Normal complement binding and opsonization (intact Fc receptor).
- There should be no prekallikrein or kallikrein activity.
- It should be tolerated by normal or hypogammaglobulinemic subjects.

Abbreviations: WHO, World Health Organization, IVIG, intravenous immunoglobulin; IgG, immunoglobulin.

subclasses IgG1, IgG2, IgG3 and IgG4 in varied proportion. In antiviral antibodies, the dominant subclass is IgG1 other subclasses are IgG2 (rubella, rabies, herpes-virus), IgG3 (rabies, rubella, cytomegalovirus {CMV}, varicella zoster, hepatitis B), and IgG4 (herpes, hepatitis B). Antibacterial antibodies are principally IgG2 type.

IVIG preparations are available in both liquid and freeze dried forms with or without stabilizers like maltose. On an average, half-life is 18–32 days. Immediately after a dose of 100 mg/kg, an average increment of 200 mg/dL results. IVIG preparations available in India include Intraglobin, Pentaglobin, Sandoglobulin, Gammaguard, Isiven VI and Octagam.

Essential Prerequisites/Requirements

Certain prerequisites must be satisfied for an IVIG preparation as per the World Health Organization (WHO) guidelines (Box 34.6).

Indications

- Prophylactic use against:
 - Measles in a leukemic child
 - Hepatitis A, especially in European children visiting developing countries
 - Hepatitis C
 - Rubella.
- IM injections can serve the purpose in all these situations.

- Replacement therapy:
 - X-linked agammaglobulinemia
 - Common variable immunodeficiency
 - Hyper-IgM syndrome
 - Immunodeficiency with thymoma
 - Severe combined immunodeficiency
 - IgG subclass deficiencies
 - Some cases of transient hypogammaglobulinemia
 - Some cases of T cell deficiency.

Children suffering from these disorders can now be led to grow up nearly normally if they receive 400–600 mg/kg of IVIG every 3–4 weeks so as to maintain IgG at 400–800 mg/dL.

- Established therapy:
 - **Immune thrombocytopenic purpura:** The established role of high dose IVIG in selected cases of ITP is detailed elsewhere Chapter 32 (Pediatric Hematology).

– **Dose:** 2 g/kg as a single IV infusion or 400 mg/kg/day IV for 5 days.

- **Kawasaki disease:** 2 g/kg as a single IV infusion or 400 mg/kg/day for 5 days.

- **Guillain-Barre syndrome:**

– **Dose:** 2 g/kg as a single IV infusion or 400 mg/kg/day for 5 days.

- Relative/Supportive therapy:

- **Autoimmune hemolytic anemia:** Therapy with high dose of 5 g/kg rather than the standard dose of 2 g/kg gives good results, especially in subjects who have undergone splenectomy.

- **Hemolytic uremic syndrome:** IVIG in a dose of 2 g/kg/day for 5 days gives good results in HUS not responsive to plasma exchange and fresh frozen plasma replacement.

- **Acquired factor VIII deficiency:** This the most common amongst the autoimmune coagulation inhibitors, may be treated with IVIG therapy in subjects who are unsuitable for combination therapy with steroids, cyclophosphamide, vincristine and cyclosporine or these who fail to respond to such a therapy.

- **Rhesus isoimmunization in pregnancy:** IVIG, 1–2 g/kg for 4–5 days, every 2–3 weeks to severely Rh-sensitized pregnant women reduces maternal anti-D titers and intrauterine hemolysis and thereby contributes to bypassing intrauterine transfusion to the baby in utero.

- It has also been reported to reduce the bilirubin level and the need for exchange transfusion in neonates with Rh-hemolytic disease.

- **Secondary immunodeficiencies:** In pediatric AIDS, IVIG is definitely of value early in the course of disease. At this stage, it prevents superadded severe bacterial infections. Later, it loses its protective value.

- IVIG is also useful in chronic lymphocytic leukemia (CLL), hypogammaglobulinemia associated with myeloma and recurrent bacterial infections following bone marrow transplantation.

- **Bone marrow transplantation (BMT):** IVIG is of value in the cellular and humoral immunodeficient state which exists in a profound magnitude in the first 4–6 months after BMT. In early post-BMT period, barrier nursing and granulocyte transfusion contributes to prevent infection more than the IVIG. In late post-BMT period, decreased IgG level with reduced antibody response causes bacterial infections and CMV infection. IVIG helps in this situation by:

- Decreasing bacterial infections, particularly capsular bacterial sepsis
- Preventing CMV infection and pneumonia.

- **Neonatal sepsis/septicemia:** There is evidence that prophylactic administration of 120 mg/kg of IVIG in a nursery with high rate of sepsis leads to a significant reduction in neonatal sepsis and mortality. Role of efficacy of such an infusion in the actual treatment of neonatal sepsis remains controversial. See Chapter 17 (Neontology).

Box 34.7 Definite indications of IVIG

- Primary antibody immunodeficiency
- ITP
- Kawasaki disease
- GBS
- Post-transfusion purpura
- Autoimmune uveitis
- Allogeneic bone marrow transplantation

Abbreviations: ITP, Immune thrombocytopenic purpura; GBS, Guillain-Barré syndrome; IVIG, intravenous immunoglobulin.

- **Pyogenic meningitis:** There is evidence that concomitant use of IVIG in patients of pyogenic meningitis on standard antimicrobial therapy contributes to better prognosis and survival. *See* Chapter 23 (Intrauterine Infections).
- **Encephalitis:** *See* Chapter 23 (Intrauterine infections).
- **Debatable indications:**
 - Allergic conditions such as asthma (severe steroid-dependent)
 - Anti-neutrophilic/nuclear cytoplasmic antibody (ANCA) positive vasculitis and rhinitis
 - Myasthenia gravis
 - Septic shock
 - Inflammatory bowel disease (IBD)
 - Kidney transplant
 - Intractable epilepsy
 - SLE (lupus crisis)
 - Hemophilia A, etc
 - Autoimmune neutropenia
 - Dermatomyositis
 - Neonatal immune thrombocytopenia.
 - Box 34.7 gives the definite indications of IVIG.

Abuse

The use of gammaglobulins is inappropriate in the following situations:

- URI in immunologically healthy children
- Physiologic hypogammaglobulinemia in newborns and preterm infants
- Malnutrition, both primary and secondary (as in protein-losing enteropathy).

Contraindications

- Selective IgA deficiency
- Recent vaccination (except hepatitis B or tetanus)
- Common variable immunodeficiency with antibodies to IgA (except selected cases with combined IgA-IgG2 or IgA-IgG4 deficiency without antibodies to IgA who may be treated).

Box 34.8 Adverse effects of IVIG

- Anaphylaxis in patients with IgG deficiency
- Chills, fever, headache, backache and arthralgia
- Dermatological reactions
- Hypertension with rise in blood urea and creatinine in patients with renal dysfunction*
- Transmission of hepatitis B and C and HIV
- Septic meningitis-like illness due to volume overload following a large dose.

Abbreviations: IVIG, intravenous immunoglobulin; HIV, human immunodeficiency virus; Ig, immunoglobulin.

*Nowadays, IVIG is available as iso-osmolar preparations. These are by and large as far as acute kidney injury is concerned with negligible risk.

Advantages of Intravenous over Intramuscular Immunoglobulin

- Very high doses can be administered.
- There is no local pain.
- There is no proteolytic degradation.
- Rise in antibody titer is rapid.
- There is no problem in administering to malnourished children and subjects with active bleeding disorder.

Hazards

Adverse reactions to IVIG (Box 34.8) may be related to the—preparation, patient, or both. Incidence is less than 5 % of the recipients.

Precautions

Strict adherence to the criteria laid down by the WHO for IVIG goes a long way in guarding against the adverse effects. While giving the infusion, the following precautions should be kept in mind:

- Start the infusion at a very slow rate—just a drop/minute and slowly increase the rate.
- If there is development of hypersensitivity reactions (chills, rigors, fever; anaphylaxis), discontinue it.

BONE MARROW TRANSPLANTATION (Hematopoietic Stem-Cell Transplantation)

Bone marrow transplantation (BMT) in the form of hematopoietic stem-cell transplantation (HSCT), carried out early in infancy, is the treatment of choice for a majority of severe cellular immunodeficiency, except ataxia telangiectasia.

The modality involves administration of marrow-ablative chemoradiotherapy and, thereafter, an infusion of either the recipient's own marrow (autologous BMT) or a donor's marrow (allogeneic BMT). For details, *See* Chapter 32 (Pediatric Hematology).

Multiple Choice Questions

- Spot the wrong observation:
 - Phagocytic response reflects destruction of the foreign agent(s)
 - About 50% lymphocytes are B cells
 - Cellular immune response ends up in destruction of the antigen
 - Figuring among functions of T killer cells is a containment of acid-fast bacilli
- All of the following are true about primary immunodeficiency, except:
 - It is far less than the secondary immunodeficiency
 - Manifestations of B cell (humoral immunity) defects include recurrent bacterial lower respiratory infection, sepsis, meningitis and nodular lymphoid hyperplasia
 - Chronic mucocutaneous candidiasis is an example of T cell defects
 - Wiskott-Aldrich syndrome is an example of neutrophil defects
- All of the following involve complement defects, except:
 - Sickle cell disease
 - Down syndrome
 - Reye syndrome
 - Malaria
- Contraindications to IVIG include all, except:
 - Selective IgA deficiency
 - Recent vaccination with the exception of hepatitis B and tetanus
 - Myasthenia gravis
 - Common variable immunodeficiency with antibodies to IgA
- None of the following statements is correct, except:
 - Absence of C1 may cause hereditary angioneurotic in the form of a swelling of the affected body part
 - Chronic granulomatous disease is characterized by extensive skin lesions that exhibit waxing and waning from early infancy
 - In IgG subgroup deficiency, total IgG level is paradoxically elevated
 - Physiological hypogammaglobulinemia usually occurs at 3–6 years

Answers

1. B 2. D 3. B 4. C 5. A

Clinical Problem-solving

Review 1

A 4-year-old child presents with chronic diarrhea, recurrent respiratory infections with one or two attacks of pneumonia every year and failure to thrive. Despite several courses of anti-giardial pharmacotherapy, infestation with *L. giardia* is persisting. Weight 11 kg, height 96 cm, mid upper arm circumference 13.5 cm.

- What is the most likely diagnosis?
- What should be the investigative approach?
- Are there more sophisticated tests?

Review 2

A 15-day-old infant with micrognathia, abnormal ears, high-arched and cleft palate, and right-sided aortic arch in imaging studies develops tetany which shows response to intravenous calcium gluconate and high doses of vitamin D.

- What is the diagnosis?
- What is its etiology?
- What is its prognosis?

Answers

Review 1

- Immunodeficiency appears to be the cause of this child's symptoms and signs, including persistent giardiasis despite several courses of appropriate therapy.
- Investigations include complete blood picture (CBP), especially TLC, DLC, and peripheral blood film; immunoglobulin levels; Schick test, opsonin function.
- Yes. These include hemagglutinin, titer, delayed hypersensitivity skin test, employing streptokinase-streptodornase, CH50 assay and NBT test.

contd...

Review 2

1. Symptoms and signs are highly suggestive of DiGeorge syndrome which results from congenital thymic hypoplasia.
2. Embryonic combined deficiency of both thymus and parathyroids (which arise from third and fourth pharyngeal pouches) in association with congenital defects of heart and aortic arch and hypoplastic mandible, defective ears and short philtrum. Hypocalcemic tetany is usually the first presenting feature.
3. Those who do not undergo spontaneous cure need thymic transplantation.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

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INTRODUCTION

Conventionally, the following six major diseases with many similarities are grouped under the class, rheumatologic disorders:

1. Rheumatic fever
2. Juvenile idiopathic arthritis (old name juvenile rheumatoid arthritis)
3. Systemic lupus erythematosus (SLE)
4. Dermatomyositis
5. Polyarteritis nodosa
6. Scleroderma.

COMMON CHARACTERISTICS OF RHEUMATOLOGIC DISORDERS

Their common characteristics are several and given in (Box 35.1). Not that the aforesaid are the only disorders of collagen. There are many more such as Ehlers-Danlos syndrome, Marfan syndrome, Stevens-Johnson syndrome (SJS), vasculitides, etc. Except for tissue damage by antigen-antibody macronodules, these immune complex diseases do not have much else in common.

ARTHRITIS: OVERVIEW

Joint pain is a common pediatric symptom. If pain is accompanied by signs of local inflammation such as (swelling, tenderness, raised temperature, limitation of movements), it is termed **arthritis** or else, it is **arthralgia**.

Arthritis may be primary or secondary to some underlying infectious or noninfectious diseases. Arthritis is labeled as **acute** when it is of less than 2 weeks duration, **subacute** when of 2–6 weeks duration and chronic when of more than 6 weeks duration (Box 35.2).

RHEUMATIC FEVER

This fairly common disease represents a hypersensitivity reaction to beta-hemolytic streptococci of Lansfield group. It is discussed in details in Chapter 27 (Pediatric Cardiology).

TRANSIENT SYNOVITIS

This is a self-limiting but common childhood condition, usually follows an upper respiratory tract infection. Clinical features include an acute onset of knees, thighs or hips lasting over a few days (usually 2–3 days). For pain relief, non-

Box 35.1

Common characteristics of rheumatologic disorders

- All involve the collagen of the connective tissue.
- Our knowledge of their exact etiology is at present far from adequate.
- Fibrinoid degeneration, granulomatous reaction with fibrosis and vasculitis with proliferation of plasma cells occur in each of them.
- There is frequently an overlapping clinical picture and chronicity with relapses.
- Changes in immunologic status are encountered.
- Improvement following steroid therapy, though often symptomatic and transitory, may occur.

Box 35.2

Classification of arthritis in childhood

Acute

- Rheumatic fever
- Kawasaki disease
- Henoch-schonlein purpura
- Transient synovitis
- Septic arthritis.

Subacute

- Reactive arthritis
- Systemic lupus erythematosus
- Dermatomyositis
- Polyarteritis nodosa
- Sickle cell disease
- Hypogammaglobulinemia
- Lyme disease
- Brucellosis
- Leukemias.

Chronic

- Juvenile idiopathic arthritis
- Tuberculous arthritis
- Perthes disease
- Ankylosing spondylitis
- Psoriasis.

steroidal anti-inflammatory drug (NSAIDs) are of value. In severe pain, skin traction may be employed.

REACTIVE ARTHRITIS

Unlike in adults, reactive arthritis is only infrequently seen in childhood. Berlin criteria are popular for its diagnosis (Box 35.3).

SEPTIC ARTHRITIS

- Mostly occurring in infants (including neonates) secondary to infections such as Gram-negative sepsis, hemophilus influenza b virus (Hib), *Streptococcus pneumonia* and *Staphylococcus aureus*.

Box 35.3 Berlin criteria for diagnosis of reactive arthritis

- Peripheral arthritis usually involving lower extremities (asymmetrical oligoarthritis).
- Evidence of preceding gastrointestinal or genitourinary infection, usually *Shigella*, *Chlamydia* or *Yersinia*, in absence of clinical manifestations.
- Exclusion of other causes of arthritis.

- Septic arthritis is characterized by monoarthritis along with local tenderness with limitation of movements and fever.
- Diagnosis is by arthrocentesis, ultrasonography, magnetic resonance imaging (MRI) and radionuclide scans.
- Therapy revolves around appropriate antibiotics and aspiration/drainage.

TUBERCULOUS ARTHRITIS

In a child with tuberculosis, tuberculous arthritis may occur in 2 ways:

1. **Monoarthritis** of ankle or hip joint as a result of direct infection of the joints.
2. **Polyarthritis** as a result of an allergic phenomenon, the so-called **Poncet's disease**.

In suspected cases, investigations for tuberculosis (at least tuberculin test, chest X-ray {CXR}, family screening) are advisable. Response to antitubercular treatment (ATT) is gratifying.

PERTHES DISEASE

This condition is characterized by avascular necrosis of the head of the femur. Mostly males aged 5–10 years are the sufferers; usually suffering from an underlying hypofibrinolysis or deficiency of protein C or protein S.

- Manifestations include a limp.
- Diagnosis is by MRI and isotope bone scans.
- Therapy is in the form of either of the following:
 - Femoral varus osteotomy
 - Containment splints.

JUVENILE IDIOPATHIC ARTHRITIS**(Juvenile Rheumatoid Arthritis)****Definition**

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease involving one or more joints and having other systemic manifestations. The disease occurs twice more frequently in girls than in boys. After the first year, it may occur at any age. However, it usually has its onset at 2–5 years in both sexes and at or around puberty in girls. Increased tendency for the disease in family members is known.

Etiopathogenesis

The exact etiology of this connective tissue (collagen) disorder is not yet precisely known. Infections, particularly with slow virus, have been blamed. Many believe that the disease

may well be an autoimmune disorder, i.e. response of antibody-forming cells to modified self-antigen.

Pathologic changes include filling of the affected joint spaces with inflammatory fluid and nonspecific inflammation of the synovial membrane. The membrane is edematous, hyperemic and invaded with plasma cells and lymphocytes. Additionally, evidence of nonspecific fibrinous serositis may also be found in pleura, pericardium and peritoneum.

Clinical Features

- The disease may have an acute or insidious onset with the variable severity.
- Most dominant manifestation is the symmetrical involvement of both small and large joints (Figs 35.1A to C), including fingers and toes (proximal interphalangeal joints), wrists, temporomandibular joints, ankles, knees, hips and cervical spine.



Figs 35.1A, B and C: Juvenile idiopathic arthritis. (A) and (B) Symmetrical involvement (inflammation) of wrists and metacarpophalangeal and interphalangeal joints giving spindle appearance to the fingers, and also involvement of ankles as well; **(C)** Involvement of knees.

- Joints are swollen, tender and warm. They have reduced mobility and are usually kept in flexion.
- In due course, contractures may result.
- A noteworthy development is the spindle-shaped fingers with shiny and smooth overlying skin. This occurs in about 1–3 months after the first involvement of the interphalangeal joints with the disease.
- Prolonged fever, usually remittent and irregular, but in some cases spiking with chills and rigors, with a morbilliform transitory rash (mainly over the trunk), muscle aches, weight loss, iridocyclitis, subcutaneous nodules, hepatosplenomegaly, lymphadenopathy, pericarditis, myocarditis, pneumonia and pleurisy are the other manifestations of the disease.
- Still disease refers to the illness with acute febrile or systemic onset. It is characterized by still triad of arthritis/arthralgia, lymphadenopathy and splenomegaly.
- In the monoarticular or pauciarticular disease with only slight systemic manifestations, almost 30% cases eventually develop chronic iridocyclitis.

Diagnosis

- **Laboratory findings** during acute phase include:
 - High total leucocyte count (TLC) (usually polymorphonuclear response) and alpha and gammaglobulin fractions of serum proteins.
 - Mild to moderate anemia is usually present.
 - Antinuclear antibodies, rheumatoid factor (which is constituted by certain macroglobulins), C-reactive protein and lupus erythematosus (LE) cell may be positive in a proportion of the cases only.
 - Rose-Waaler test is positive in a large majority of the cases.
- **X-ray findings** in the early stages include swelling of periarticular soft tissue, effusion, slight increase in the joint spaces, increase in size of ossification centers, accelerated epiphyseal maturation and excessive longitudinal bone growth. Later, destruction of articular cartilages causes narrowing of the joint space. Disuse may lead to osteoporosis and deformities. There may also be radiologic evidence of cervical spondylitis.
- **Synovial fluid** may show an inflammatory reaction.
- **Synovial biopsy** shows chronic inflammation which is, however, not pathognomonic for rheumatoid arthritis.
- Electrocardiogram (ECG) is indicated in suspected cardiac involvement.
- **Echocardiography** may detect pericarditis in a high proportion of cases.

Differential Diagnosis

Differential diagnosis is mainly from rheumatic fever, SLE, leukemia and ulcerative colitis in case of pauciarticular disease and septic arthritis, traumatic synovitis and tuberculosis in case of monoarticular disease.

Table 35.1: Recommended NSAIDs in pediatric JIA

Drugs	Doses	Major side-effects
Naproxen	15–20 mg/kg/day in 2 divided doses	Skin rash, gastritis, constipation, dizziness, headache, drowsiness
Ibuprofen	30–50 mg/kg/day in 4 divided doses	Gastritis, hypertension, tachycardia, fluid retention, acute renal failure
Indomethacin	1–2 mg/kg/day in 3 divided doses	Nausea, vomiting, epigastric pain, GI bleeding, icterus, headache
Diclofenac	2–3 mg/kg/day in 4 divided doses	GI upset, neurological manifestations
Piroxicam	0.3–0.6 mg/kg/day only once a day	Nausea, anorexia, rash, pruritus, heartburn, edema, CNS manifestations
Tolmetin	15–30 mg/kg/day in 3–4 divided doses	Gastritis, hypertension, headache, tinnitus, fluid retention, acute renal failure

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; JIA, juvenile idiopathic arthritis; CNS, central nervous system; GI, gastrointestinal.

Treatment

Drug Therapy

- **Nonsteroidal anti-inflammatory drugs:** Today, NSAIDs, namely ibuprofen, naproxen and indomethacin, diclofenac, piroxicam and tolmetin are the recommended therapy for pediatric juvenile rheumatoid arthritis (JRA). Their effective anti-inflammatory dose is usually 2–3 times the analgesic dose (Table 35.1). Response usually occurs after 3–4 weeks. A 4–6 weeks therapy is essential before considering change of drug. In view of gastrointestinal adverse drug reactions (ADRs) of NSAIDs, therapy should be monitored.
- **Steroids:** Corticosteroids are indicated in the following situations:
 - Complications such as carditis, pericarditis, pleuritis and iridocyclitis
 - Life-threatening disease
 - Failure to respond to other NSAIDs over a sufficiently reasonable period
 - Progressive deformities
 Intra-articular steroid therapy deserves trial when one or two joints are involved and they retard rehabilitation of the child.
- **Disease modifying anti-rheumatic drugs (DMARDs):** Methotrexate (MTX), 15–20 mg/m² (O) once a week, should be considered the drug of choice in JRA not responding to NSAIDs.
- **Slow acting anti-rheumatic drugs (SAARDs):** Gold salts, D-penicillamine and hydroxychloroquine need to be reserved as **add-on** or adjunctive therapy for JRA failing to respond to MTX.
- **Biologicals:** The new agents (Box 35.4) are finding increasing role in difficult cases of JIA.

Box 35.4 Biologicals in severe JIA

- IL-1 receptor antagonists: Anakinra
- Monoclonal antibodies to IL-1: Canakinumab
- Monoclonal antibodies to IL-6 receptor: Tocilizumab
- Monoclonal antibodies to TNF-alpha: Infliximab, golimumab, adalimumab
- Recombinant soluble TNF receptor p75 fusion protein: Etanercept
- Inhibitor of T cell activation: Abatacept.

Abbreviations: IL, interleukin; NSAIDS, nonsteroidal anti-inflammatory drugs; JIA, juvenile idiopathic arthritis; TNF, tumor necrosis factor.

General Measures

- The role of physiotherapy is significant in the management. During acute illness, the child must rest in bed with appropriate positioning of the involved joints. Exercise (first assisted, then active and finally resisted) once or twice daily is mandatory even during acute phase.
- For relief of pain, the child should be encouraged to take hot bath.
- Emotional support and reassurance should be provided to the child as well as the parents.
- Superimposed infection should be promptly controlled lest it reactivates the disease during convalescence.

Complications

- Chronic anemia
- Chronic anterior uveitis
- Macrophage activation syndrome
- Limb length discrepancies
- Contractures
- Growth failure
- Secondary amyloidosis.

Prognosis

With adequate care, a large majority of the patients have complete functional recovery.

SYSTEMIC LUPUS ERYTHEMATOSUS

This highly multisystem collagen disorder is predominantly seen in girls. The occurrence in children under 8 years is infrequent.

Pathology

Pathologically, the hallmarks of the disease are fibrinoid degeneration and necrosis which are found extensively. A characteristic feature is the circulation of autoantibodies which produce the typical LE cell in the bone marrow. This cell is polymorphonuclear leucocyte. It contains metachromatic inclusion body which displaces the nucleus.

Clinical Features

- The onset is gradual with prolonged, irregular fever with remissions of variable duration
- Joint or muscle pains, malaise and weight loss
- Characteristic erythematous rash resembling the wings of a butterfly (butterfly rash) over the bridge of



Fig. 35.2: Systemic lupus erythematosus. Note the butterfly rash over face.

the nose and cheeks (Fig. 35.2). Rash may also appear on fingers and palms, soles, palate and buccal mucosa.

- Alopecia may also be found.
- The disease does not spare any organ. Renal involvement, neurologic manifestations, polyarthritis, pericarditis, pleural effusion, pulmonary infiltration, thrombocytopenia, hepatosplenomegaly, generalized lymphadenopathy, abdominal pain, vomiting and diarrhea may occur.

Diagnosis**Laboratory Work-up**

- Lupus erythematosus preparation (Figs 35.3 and 35.4)
- Serology It is confirmed by demonstrating antinuclear antibodies (ANA) which is a more sensitive test than the LE preparation (Box 35.5).

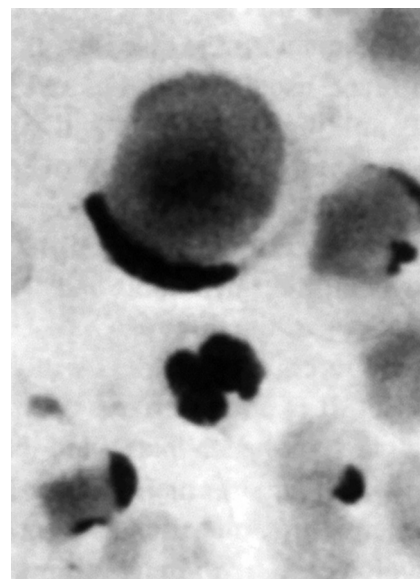


Fig. 35.3: Systemic lupus erythematosus. Photomicrograph of peripheral blood highlighting a classical LE cell.

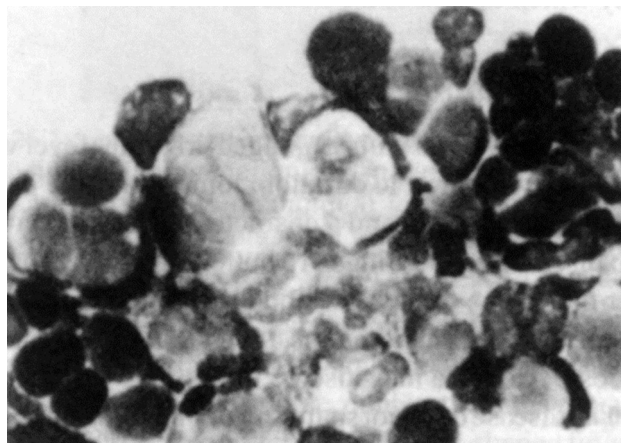


Fig. 35.4: Systemic lupus erythematosus. Photomicrograph of peripheral blood showing a cluster of LE cells and hematoxylin bodies along with multiple small inclusions.

Box 35.5 Serology in SLE; Various markers

- **Anti-Sm antibodies:** CNS lupus
- **Anti-Ro/SSA and anti-La/SSB:** Congenital heart blocks seen in neonatal lupus syndrome
- **Anti-double-stranded DNA antibodies:** Active SLE
- **Antihistone antibodies:** Drug-induced lupus erythematosus because of agents such as isoniazid, hydralazine or diphenylhydantoin.

Box 35.6 Diagnostic criteria for SLE

- Malar rash—a rash over the cheeks and nose, often in the shape of a butterfly
- Discoid rash—a rash that appears as red, raised, disc-shaped patches
- Photosensitivity—a reaction to sun or light that causes a skin rash to appear or get worse
- Oral ulcers—sores appearing in the mouth
- Arthritis—joint pain and swelling of two or more joints in which the bones around the joints do not become destroyed
- Serositis—inflammation of the lining around the lungs (pleuritis) or inflammation of the lining around the heart that causes chest pain which is worse with deep breathing (pericarditis)
- Kidney disorder—persistent protein or cellular casts in the urine
- Neurological disorder—seizures or psychosis
- Blood disorder—anemia (low red blood cell count), leukopenia (low white blood cell count), lymphopenia (low level of specific white blood cells) or thrombocytopenia (low platelet count)
- Immunologic disorder—anti-DNA or anti-Sm or positive antiphospholipid antibodies
- Abnormal antinuclear antibody (ANA).

Abbreviations: SLE, systemic lupus erythematosus; DNA, deoxyribonucleic acid.

Diagnostic Criteria

Box 35.6 list the diagnostic criteria. Only 43 of these 11 criteria are required for diagnosis of SLE.

Treatment

Asymptomatic patients need not be given any treatment. In mild cases (without renal involvement), NSAIDs suffice. In the presence of acute inflammatory manifestations,

steroids are indicated. This therapy suppresses these manifestations. It may also inhibit progressive renal disease.

Chloroquine is of value for skin and joint manifestations. Generally speaking, steroids and hydroxychloroquine are the life line of therapy of SLE. As rule, prednisolone is the drug of choice among steroids for most symptomatic cases. To begin with, it is given , 1–2 mg/kg daily. Once the patient becomes stable, it is tapered over several months. Antibiotics should be given as and when infection is suspected. Sunscreen lotions are recommended. Life-threatening manifestations are an indication for intravenous (IV) pulses of steroids (methyl prednisolone) followed by oral steroids. Patients resistant to steroid therapy may respond to immunosuppressive agents such as azathioprine cyclophosphamide, ritiximab, mycophenolate mofetil, etc.

An important caution in management is to avoid the use of drugs that as known to produce lupus-like picture or precipitate SLE. Hydralazine, anticonvulsants, long acting sulfas and methyldopa figure in that list. Low dose prednisolone plus hydroxy chloroquine need to be continued over many years. The so-called antiphospholipid (APL) syndrome is a frequent comorbidity seen in SLE (also in other rheumatological conditions).

Prognosis

With good medical management, survival rate for 5 years is now around 80%. Common causes of mortality are progressive glomerulonephritis, myocarditis and CNS involvement (encephalopathy).

DERMATOMYOSITIS

This rare chronic inflammatory disease of unknown etiology affects mainly the skin, subcutaneous tissue and muscles. The basic lesion is vascular, leading to arteritis and phlebitis.

- The onset is insidious. Clinical picture includes fever, muscle tenderness, pain, weight loss, malaise, pseudoparalysis, arthralgia and an erythematous rash. The rash first develops over the bridge of the nose and around eyes and then anywhere over trunk and limbs. An edematous swelling of the malar area and visible capillaries in the nailbed and gum margin are highly suggestive findings. Eventually, the involved muscles become firm, atrophic and contracted. Calcinosis may occur. The face may develop an expressionless appearance, the child hardly being able to fully open the mouth.
- In a suspected case, high levels of muscle enzymes, a myopathic electromyography (EMG) and muscle biopsy revealing chronic inflammatory changes may support the diagnosis.
- As soon as that diagnosis is made, the child must receive steroids. Azathioprine or methotrexate may be tried if response to steroids is poor. Physiotherapy and occupational therapy are important.
- With this treatment, prognosis in childhood dermatomyositis is good in a majority of the cases, provided that the therapy has been started fairly early.

700 POLYARTERITIS NODOSA (Periarteritis)

This, another very rare systemic disorder, is characterized by inflammatory lesions in the arterial wall, leading to ischemia from thrombosis.

- Clinical picture varies with the location of the affected arterioles. The manifestations are usually those of a rapidly progressive wasting disease. These may include fever, weight loss, generalized body pains, abdominal pain, skin eruptions, subcutaneous nodules, hypertension, hematuria, convulsions, paralysis, congestive cardiac failure (CCF) or ischemic gangrene of a limb.
- Muscle, testicular or skin biopsy may support the clinical diagnosis.
- Steroids may produce dramatic response and prolong life, but the results are unpredictable and variable. However, cyclophosphamide started concurrently, needs to be continued on long-term basis.
- The occurrence of renal, cardiac or neurologic involvement usually indicates a poor prognosis.

SCLERODERMA

This rare disorder is characterized by thickening and induration of the skin from deposition of collagen fibre.

Clinical Features

- Systemic manifestations are minimal.
- It usually begins in the face, forearm and hands and may or may not spread elsewhere.
- Because of development of contractures, face becomes masklike, just as in dermatomyositis.
- Trophic ulcers, calcinosis and Raynaud phenomenon may occur.
- Involvement of gastrointestinal tract (GIT) may cause malabsorption.
- Lesions in the esophagus may lead to obstruction and dysphagia.
- A localized form of scleroderma, *morphea*, is characterized by linear band that first shows erythema and edema and later undergoes atrophy, scarring and shrinking.

Differential Diagnosis

It is from scleredema, phenylketonuria (PKU), porphyria cutanea tarda and progeria (together termed *pseudosclerodermas*).

Treatment

Morphea responds well to physiotherapy, leaving little or no deformity. Generalized scleroderma (sclerodactylia) has only fair prognosis. Death may occur within a year. Drug therapy includes penicillamine, cochlincine, pulse steroids, nifedipine and enalapril, etc. A 10-year survival rate is possible in 90% of the pediatric subjects.

MIXED CONNECTIVE TISSUE DISEASE

- Mixed connective tissue disease (MCTD) is a cocktail of features of SLE, rheumatoid arthritis and dermatomyositis.
- Anti-ribonucleoprotein (RNP) antibodies are quite high while anti-DNA antibodies, anti-extractable-nuclear antigens (anti-ENA) are positive.
- Response to NSAIDs and steroids is variable.

GOODPASTURE SYNDROME

This condition, only occasionally seen in pediatric practice, is characterized by pulmonary alveolar hemorrhage (clinically presenting as hemoptysis and secondary anemia) and nephritis.

- Accompanying manifestations may include dyspnea, cough and pyrexia. Progressive renal failure is common.
- Despite therapy with agents such as steroids, alkylating agents and metabolites, the syndrome has a rapidly fatal outcome.

FASCITIS

(Eosinophilic Fascitis)

Diffuse inflammation of the fascial tissues of the extremities and trunk, usually following periods of strenuous physical exertion, may occasionally occur in children. Overlying skin remains unaffected. Besides swelling and tenderness of the affected area, loss of musculoskeletal function and contractures may occur.

Remarkable increase in eosinophils in blood as well as in involved tissues is seen in some subjects. Hence, the other name *eosinophilic fascitis*. Steroid therapy may expedite recovery.

BENIGN RHEUMATOID NODULES

Subcutaneous nodules may occasionally be seen without any evidence of rheumatic disease (clinical or even investigative) in absolutely healthy children. These show a tendency for waxing, waning and recurrence. In due course varying from months to years, recurrences stop. This is a benign condition. It needs no therapy.

VASCULITIS SYNDROMES

(Vasculitides)

In this entity, there is an inflammation of the vasculature. Depending on involvement of large, medium or small sized blood vessels, three groups are recognized (Box 35.7).

KAWASAKI DISEASE

(Mucocutaneous Lymph Node Syndrome, Infantile Polyarteritis)

First described in 1967 by Kawasaki of Tokyo, it has emerged as an important cause of vasculitis and heart disease in children. It is primarily a disease of children 5 years of age or younger, occurring worldwide, sporadically or in epidemics.

Box 35.7 Three groups of pediatric vasculitides**1. Large vessel vasculitis**

- Takayasu arteritis
- Giant cell arteritis

2. Medium vessel vasculitis

- Kawasaki disease
- Polyarteritis nodosa

3. Small vessel vasculitis

- Anaphylactoid purpura (Henoch-Schoenlein purpura)
- Wegener granulomatosis
- Behcet disease
- Hypersensitivity angitis.

Definition

Kawasaki disease is defined as an acute febrile vasculitis characterized by mucocutaneous and lymph node involvement occurring primarily in infants and children upto 5 years of age.

Etiology

Exact etiology of Kawasaki disease is not yet known. Epidemiological as well as clinical picture points to an infectious cause. The role of retroviruses or rickettsia as

also immune aberrations are major factors in its causation has not been established. **701**

Clinical Features (Figs 35.5A to F)

- Unexplained irritability is the earliest manifestation.
- Prolonged high fever, conjunctivitis, stomatitis, strawberry tongue, fissured lips, cervical adenopathy and macular erythema with pronounced reddening of the palms and soles; dorsum of hands may also be swollen; subsequent desquamation of the digits (periungual desquamation). Nails may show peculiar transverse line (Beau line).
- Diarrhea, vomiting and abdominal pain, etc.
- Hydrops of gallbladder, nerve palsies, seizures, myositis, tympanitis, rhinorrhea, cough, hepatosplenomegaly, iridocyclitis (on slit lamp examination) and large artery aneurysms are other manifestations.
- Manifestations of cardiac involvement include coronary vasculitis (ischemia, infarction or rupture of aneurysm), myocarditis, endocarditis, pericarditis, heart failure and arrhythmias.
- Arthralgia/arthritis, pyuria, proteinuria, mild hepatitis and aseptic meningitis may occur.



Figs 35.5A to F: Kawasaki disease. (A) Typical rash involving face; (B) Typical rash involving body; (C) Typical rash involving palms; (D) Typical strawberry tongue; (E) Conjunctivitis; (F) Peeling of skin.

Box 35.8 Diagnostic criteria for Kawasaki disease**Essential**

- Fever lasting for a minimal of 5 days
- Illness not explained by any other known disease process.

Nonessential (4 of the 5 features suffice)

- Bilateral nonpurulent conjunctival injection
- Changes of the mucosa of the oropharynx, including infected pharynx, infected and/or dry fissured lips, strawberry tongue
- Changes of the peripheral extremities, e.g. edema and/or erythema of hands or feet, desquamation, usually beginning perungually
- Rash (primarily truncal, polymorphous, but always nonvesicular)
- Cervical lymphadenopathy (at least one node >1.5 cm); it is usually unilateral.

Diagnosis

Laboratory findings include mild anemia, leucocytosis, raised erythrocyte sedimentation rate (ESR), raised C-reactive proteins, normal antistreptolysin O (ASO) titer, thrombocytosis, high levels of circulating immune complexes and hypergammaglobulinemia. Tests for rheumatoid factor and antinuclear antibodies are negative. Serum complement levels are normal or slightly elevated.

Cardiac studies must include 2D echocardiography at time of first presentation and then after 2 weeks for detecting coronary dilatation or aneurysm. Diagnosis is more or less clinical and should rest on the demonstration of certain criteria (Box 35.8).

Differential Diagnosis

It is from infectious diseases such as infectious mononucleosis, poststreptococcal disease, Stevens-Johnson syndrome, toxic shock syndrome, leptospirosis, JRA, measles, and other vasculitic syndromes.

Treatment

Currently, the treatment of choice is high dose intravenous immunoglobulin (IVIG) 2 g/kg as a single dose over 10–12 hours or IVIG 400 mg/kg/day for 5 days. The response is dramatic. Moreover, it also prevents coronary vascular involvement.

During the febrile phase, the subject should also be given salicylates (aspirin) 75–100 mg/kg/day in divided dose as long as the child does not become afebrile. Later salicylate therapy should be continued in low, single-dose 5 mg/kg/day for 6–8 weeks after the active disease has subsided to benefit from its antiplatelet activity.

If coronary lesions are already present, this therapy with or without dipyridamole needs to be carried on until the coronary involvement has regressed. Besides mainstay therapy, following approaches may be in places in certain situations:

- Heparin or warfarin therapy may be added in case of large aneurysms.
- Streptokinase therapy is indicated in case of active phase of coronary artery thrombosis.
- Prostaglandin E infusion is indicated in peripheral artery ischemia.
- Symptomatic children with gross stenotic lesions may be subjected to aortocoronary bypass surgery.

Prognosis

The disease is generally benign and self-limiting, regressing in one to several weeks. In some cases, however, there may occur cardiovascular involvement in the form of myocarditis, pericarditis, coronary aneurysms, coronary thrombosis and myocardial infarction, causing mortality in 0.5–2.8% cases. Incidence of coronary artery disease in untreated cases is in the range of 20%.

HENOCH-SCHONLEIN PURPURA**(Anaphylactoid Purpura)**

It is a self-limiting systemic vasculitis involving skin, joints, GIT and kidneys, etc. For details about the IgA-mediated disorder, *See* Chapter 32 (Pediatric Hematology).

POLYARTERITIS NODOSA

It stands discussed earlier in this very chapter.

BEHCET DISEASE

This very rare vasculitis is characterized by aphthous stomatitis, skin lesions, genital ulceration, ocular problems, thrombophlebitis, arthritis, cardiovascular and neurologic disease, resulting in considerable disability. Response to steroids and/or chlorambucil is variable.

TAKAYASU ARTERITIS

See Chapter 27 (Pediatric Cardiology).

GRANULOMATOSIS WITH POLYANGITIS**(Wegener's Granulomatosis)****Definition**

This very rare syndrome is characterized by necrotizing granulomatous lesions of the respiratory tract and lungs along with a systemic necrotizing vasculitis that is most remarkable in lungs and kidneys.

Diagnosis

An important diagnostic investigation is antineutrophil cytoplasmic antibodies (ANCA).

Differential Diagnosis

It is from other vasculitides, lymphoma, tuberculosis, allergic alveolitis, Goodpasture syndrome (described earlier in this Chapter) and fungal infections.

Treatment

Response to steroids and cyclophosphamide is gratifying.

MARFAN SYNDROME

See Chapter 47 (Pediatric Orthopedics).

EHLER-DANLOS SYNDROME

See Chapter 36 (Pediatric Dermatology).

Multiple Choice Questions

- Which disease is incorrectly matched with the characteristic rash?
 - Systemic lupus erythematosus Malar rash sparing nasolabial fold
 - Discoid-Lupus Hyperkeratotic rash around the ears
 - Kawasaki disease Vesicular rash
 - Henoch-Schonlein purpura Palpable purpuric rash over the extremities and over the buttocks
 - Juvenile dermatomyositis Gottron papules and heliotrope rash
- Most appropriate observation regarding organisms associated with reactive arthritis:
 - Shigella
 - Chlamydia trachomatis*
 - Yersinia enterocolitica*
 - Campylobacter jejuni*
 - All of the above
- A 15-year-old very tall girl is noted to have lax joints, dislocation of lens and mitral valve prolapse. The most likely diagnosis is:
 - Acromegaly
 - Ehler-Danlos
 - Marfan's syndrome
 - Myotonic dystrophy
 - Homocystinuria
- All these are true about Reiter's syndrome, except:
 - Characterized by triad of arthritis,conjunctivitis and urethritis
 - Affected ones are usually HLA-B27 positive
 - Arthritis affects a few joints
 - Does not respond to treatment
 - Usually follows a diarrheal illness
- Most likely cause of limping of several days duration in an obese boys with limitation of internal rotation and abduction:
 - Congenital dislocation of hip
 - Perthes disease
 - Septic arthritis
 - Slipped femoral capital epiphysis
 - Toxic synovitis
- All these statements are true, except:
 - Uveitis can lead to vision loss
 - Transient synovitis is self-limiting regressing in a few days without any treatment
 - Arthritis is a common complaint in children
 - Tuberculous arthritis is very common in children
- A combination of 7 days' fever, conjunctivitis lymphadenopathy and generalized rash in a 3-year-old is suggestive of diagnosis of:
 - Acute rheumatic fever
 - Kawasaki disease
 - Lyme disease
 - Rubella

Answers

- | | | | | | |
|------|------|------|------|------|------|
| 1. C | 2. E | 3. C | 4. D | 5. D | 6. D |
| 7. B | | | | | |

Clinical Problem-solving

Review 1

A 5-year-old girl develops a widespread purpuric rash, most prominent over the legs and buttocks. Earlier, the child was treated with IV antibiotics for 48 hours suspecting meningococcal sepsis. Now, this diagnosis is deferred as there is no evidence of infection. Later, girl becomes afebrile but is reluctant to bear weight on legs. She also complains of abdominal pain.

- What is the most likely diagnosis in this girl?
- What is the prognosis in this condition?
- What percentage of these patients end with renal problems?
- What about its follow-up?

contd...

Review 2

A 2-year-old girl presents with high temperature (one or two daily spikes of 39–40°C). During the febrile episodes child becomes very listless and sick. Also, she develops a pink rash over the trunk, face, palms and soles. Examination, shows generalized lymphadenopathy, hepatosplenomegaly and tender swelling of knee joint.

Lab investigations show leukocytosis (WBC-36,000/mm³), raised CRP and anemia (Hb 8 g/dL).

1. What is the most likely diagnosis in this child?
2. What cardiac studies should be carried out?
3. What should be the treatment?
4. How about the prognosis?

Answers**Review 1**

1. The most likely diagnosis in this child is Henoch-Schonlein purpura (HSP). This is the most common form of vasculitis occurring in pediatric patient.
2. Usually, HSP has a benign course.
3. A minority (just 5%) of cases may develop a long-term renal compromise (including end-stage renal failure). About 1% may go on to develop total kidney failure.
If significant renal failure is going to occur it usually does so within the first year of life following an acute episode of HSP.
4. A regular urinalysis and blood pressure monitoring is essential for about one year.

Review 2

1. Kawasaki disease.
2. The 2-dimensional echocardiography at time of first presentation and then after 2 weeks for detecting coronary dilatation or aneurysm.
3. Currently, treatment is high dose IVIG, 2g/kg as a single dose over 10–12 hours or 400 mg/kg/day for 4 days. Additionally, aspirin needs to be given for 6–8 weeks—first high dose during febrile phase and then low dose.
4. In most cases, it is a self-limiting disease, regressing in one to several weeks. In the event of cardiovascular complications, 0.5–2.8% mortality may occur.

FURTHER READING

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INTRODUCTION

Approximately 30% of pediatric outpatient department (OPD) attendance is accounted by dermatologic disorders as such or as associates of other illnesses. Skin may also be an index of many systemic and genetic disorders. A vast majority of skin problems may be categorized as allergic (atopic dermatitis), infective (bacterial, viral, fungal, parasitic), vascular (hemangiomas, urticaria), pigmentary (vitiligo), scaly and hormonal (acne vulgaris).

MORPHOLOGY OF SKIN LESIONS

A skin lesion may be primary or secondary. Examples of **primary lesion** include macule, papule, vesicle and pustule. A **secondary skin lesion** such as crust, scale, ulcer, fissure, erosion, atrophy and lichenification (additional lesions on top of a papule) develops from a primary lesion. Table 36.1 lists various morphological lesions along with their brief definitions.

ATOPIC DERMATITIS

Atopic dermatitis, a chronic skin disease characterized by erythema, exudation, lichenification and intense pruritis, usually begins in the first few months of life. In view of its known association with hay fever (allergic rhinitis), asthma and immunodeficiency, it has been suggested that it may well be a late phase immunoglobulin (IgE)-mediated reaction as a result of a constitutional anomaly in the immune system.

Clinical Features

Atopic dermatitis has varied presentation.

- When it manifests before 3 months of age, the characteristic lesions are erythematous squamous patches that first appear over the scalp, behind the ears, around the nose, buttocks or genitalia (Fig. 36.1). This, the so-called **seborrheic dermatitis**, as rule, resolves in 4–6 weeks. In a small proportion, it may progress to infantile eczema.
- In **infantile eczema**, rosy erythema of the cheeks is outstanding. In addition, there is fissuring of the skin folds behind the ears, soddening of the neck folds, dryness and scaling of the extensor surfaces of arms, wrists and legs. Itching is remarkable, the scratching leading to excoriation and secondary infection (both bacterial and with *Candida*). Note that periorbital, perioral, nasal areas and buttocks are usually spared in infantile eczema. Following a course of remissions and exacerbations, spontaneous remission occurs in a majority of the cases by 1–2 years of age.

- In **late-onset atopic eczema** or in infantile eczema that continues after 1–2 years of age, anterior of neck, flexures of elbows and knees and front of ankles show erythema, scaling and lichenification. This is termed **flexural eczema**.
- Atopic dermatitis may also manifest as **nummular eczema** (coin shaped vesicular lesions with severe pruritis), or **pityriasis alba** with hypopigmented patches over face.

Diagnosis

For diagnosis of atopic dermatitis—3 major and 3 minor criteria (Box 36.1) must be satisfied.

Treatment

It comprises of topical low concentration steroid and antibiotic cream and antihistaminic drugs. A short course (7–10 days) of systemic antibiotics is warranted in active disease. Supportive measures include:

- Gentle bathing with a small amount of liquid antiseptic soap.
- Cutting the nails short to prevent scratching trauma.
- Avoidance of nonspecific allergens like dust, nylon, feathers and animal dander.
- Avoidance of suspected food allergen.

Infants and children with atopic dermatitis are likely to have higher incidence of bronchial asthma. Even apparently asymptomatic children stand good chances of manifesting symptoms of asthma under stress and strain.

INSECT BITE HYPERSENSITIVITY

During summer and rainy season, quite a proportion of children with insect bite, including mosquito and bedbugs, have a tendency to develop intensely pruritic lesions (pustules, papules) over exposed areas. Treatment consists of local application of steroid cream/ointment.

DRUG ERUPTION

Logically speaking, all drugs are capable of causing an eruption, which is usually exanthematous. Nevertheless, the drug notorious in this behalf is sulfonamides, penicillin's, anticonvulsants and antituberculous drugs. Drug eruption is usually a symmetrical itchy macule or papule which quickly spreads to the whole of the skin, including palms and soles, and at times, the mucosal surface too (Fig. 36.2). The initial discrete lesions have a tendency to coalesce to form large patches. Left unattended, the lesion may further spread, ending up as exfoliative dermatitis. Fever and itching may accompany the rash.

Table 36.1: Various morphological skin lesions along with their brief definitions

Primary lesions	Short description
Macule	Well defined, but flat lesions with a change in color
Patch	A macule larger than 1 cm in size
Papule	Raised and palpable solid lesion, smaller than 5mm
Nodule	A large papule, usually 5–10 mm in diameter
Plaque	A raised flat-topped lesion on skin or mucous membrane, usually over 1 cm in size
Blister	A small bubble on the skin filled with serum and caused by friction, burning, or other damage.
Vesicles	Raised fluid-filled lesion
Pustule	Pus-containing well-circumscribed lesion
Abscess	A thick-walled pus-filled cavity developed from necrosis of tissue
Wheal	A whitish, firm and elevated lesion surrounded by red flare as a result of dermal edema
Petechiae	A circumscribed deposit of extravasated blood, less than 5 mm in diameter
Purpura	A circumscribed deposit of extravasated blood, more than 5 mm in diameter
Echymosis	A blend of several petechiae and purpuric spots, occupying a large area of skin
Telangiectasia	A visible dilatation of superficial blood vessels
Poikiloderma	A triad of atrophy of skin, reticular pigmentation, and telangiectasia
Cyst	A circumscribed lesion having a wall and a lumen containing fluid or solid matter
Comedone	An inspissated plug of sebaceous and keratinous material lodged in a dilated orifice; close white and open black types are known
Milia	A small subepidermal keratin cyst that is a normal finding in neonates
Burrow	A thread-like elevated tortuous channel in the skin typically seen in scabies.
Secondary lesions	Short description
Scale	A visible flake comprising shed stratum corneum (horny layer) of the skin
Crust	A collection of dried serum and cellular debris
Erosion	A focal breach in the continuity of epidermis with preservation of dermis, leaving no scarring after healing
Ulcer	A focal breach in the continuity of epidermis as well as upper dermis
Fissures	A linear slit-like breach in epidermis as well as dermis (full layer, not just the upper dermis)
Excoriation	A linear erosion or ulcer caused by scratching
Atrophy	A thinning of epidermis, dermis or subcutaneous tissue
Scar	A formation of connective tissue that replaces the original skin. Normal skin markings are absent in scar
Sclerosis	A circumscribed or diffuse. An area of induration and binding down of skin
Lichenification	An area of skin that is thickened along with hyperpigmentation and enhanced skin markings due to repeated scratching.



Fig. 36.1: Atopic dermatitis. Highly pruritic erythematous papules, especially of the face, are the hallmark of this condition.

Box 36.1**Diagnostic criteria for atopic dermatosis****Major**

- Pruritus
- Distribution over face and convexities in infants under 2 years and over flexures in older children
- Tendency to chronicity
- Personal or family history of atopy.

Minor

- Immediate skin test reaction
- Delayed blanching to cholinergics
- Anterior subcapsular cataract
- Xerosis
- Ichthyosis vulgaris with an accentuation over palmar creases
- Facial pallor/suborbital shadowing
- Infraorbital folds
- Keratoconus
- Recurrent skin infections
- Tendency to nonspecific dermatosis of hands
- Raised serum immunoglobulin (IgE).



Fig. 36.2: Fixed drug eruption. It classically occurs at the same site if the subject is exposed to the same medication. Hence the name. It is believed to be mediated through type IV hypersensitivity.

Immediate withdrawal of the offending drug leads to regression (or at least no further progression) of the drug eruption. In addition to withdrawal of the causative drug (all drugs being taken by the child in case there is doubt as to which one is responsible for eruption), it is beneficial to administer systemic steroids for a week or so. Antihistaminics provide only symptomatic relief from itching.

SCABIES

(Seven-year Itch)

It is caused by an insect mite, *Sarcoptic scabiei*, and is spread by skin to skin contact. No age is immune.

Clinical Features

- The characteristic skin lesions are papules and vesicles that involve the skin, usually below the neck.
- The usual sites are between fingers and toes, ulnar side and front of wrist, elbow, anterior axillary fold, buttocks, umbilicus and male genitalia.
- Warm and moist locations of the body are generally affected.
- Unlike adults, infants and children may suffer from lesions over face and scalp. Lesions over palms and soles may also occur (Fig. 36.3).
- Intense itching and superadded infection may cause formation of pustules which, if not treated, lead to more widespread lesions with somewhat changed appearance and even development of crusts.
- Acute nephritis may occur as a complication of scabies. Also See Chapter 31 (Pediatric Nephrology).

Diagnosis

Generally, a clinical diagnosis is considered sufficient for prescribing specific therapy. Burrows are considered



Fig. 36.3: Scabies. Eczematous lesions in the form of papules and nodules are evident. Rather than interdigital lesions, infants more often have lesions over face, scalp, palms and soles. Thread-like burrows too are infrequent in infants.

pathognomonic for scabies. Confirmation of the diagnosis is by demonstration of the mite microscopically in the scrappings obtained from burrows, eczematous lesions or fresh papules. The method consists of pouring a drop of a mineral oil on a lesion. With a dull-edged tool, this is vigorously scrapped. Then, the oil and the scrappings are transferred to a glass slide. Under the microscope, the mite is easily identified by its movements.

Treatment

Permethrin 5% cream is now considered to be the best scabicide for infants over 2 months and children. Since it is poorly absorbed and rapidly metabolized by tissue esterases, its toxicity is practically negligible. Crotamiton, gamma benzene hexachloride, mesulphen, sulfur and dichlorodiphenyltrichloroethane (DDT) are also effective.

Treatment with 25% benzyl benzoate, diluted in calamine or water in case of small children, all over the body from neck to toes, after preliminary bath is only infrequently practiced. In case of infected scabies, it is desirable to treat the infection with a suitable chemotherapeutic agent prior to treatment with a scabicide agent. After the treatment, all clothing, bed linens and towels should be laundered thoroughly (boiled, sunned and ironed).

All contacts should also receive treatment simultaneously, even if they have no overt lesions. Ivermectin*, 200 µg/kg (O), given in 2 doses, one week apart has yielded gratifying results. Persistent pruritus, even after the skin lesions have disappeared following specific therapy, is usually the result of hypersensitivity to the mite antigen. It should not be interpreted as a failure of treatment. Topical steroid assist in alleviating it. Nodular lesions of scabies may take several months to disappear.

* Ivermectin is effective in some intestinal parasitic infestations as well.



Fig. 36.4: Pediculosis. Note the urticated papules at the nape of the neck. It is a sound principle to search for pediculi and nits in the scalp in such a presentation.

PEDICULOSIS

Louse infestation of the hairy regions is a common problem in the low socioeconomic group whose personal hygiene is poor.

Three forms of the disease, depending on the body region involved, are known:

1. Pediculosis capitis (head involvement)
2. Pediculosis corporis (body involvement)
3. Pediculosis pubic (pubic involvement).

Pediculosis capitis is the one most frequently encountered. It is relatively more common in the females. The most common complaint is intense itching in patches of hairy regions and nearby areas, say nape of the neck, provoking scratching (Fig. 36.4). Scratching causes localized areas of excoriation which very often get infected, causing regional lymphadenitis. The parasite is seen as an elongated nit (egg) near the root of the hair or as an adult louse—many a times almost overcrowding the hairy area.

Treatment consists of local application of DDT (5%), benzyl benzoate (12.5%) or permethrin (5%). The hair should be left as such for a few days after application of the medicine. Then it should be washed. Resistant or heavy infestation may need one or two more applications at weekly intervals. If superadded infection exists, it must be treated before applying DDT, benzyl benzoate, or permethrin.

RINGWORM INFECTIONS

(Dermatophytosis, Dermatophycosis)

Dermatophytes, the highly specialized fungi, may cause a variety of lesions of skin and its appendages. In Kashmir, incidence of ringworm infections is fairly high.

Tinea capitis consists of seborrhea-like scaly and circumscribed patches. In advanced cases, alopecia occurs (Fig. 36.5). It responds well to oral griseofulvin, 20 mg/kg/day for 5–7 days. Topical application of an antifungal cream (Whitfield, for instance)—in addition to the oral therapy—is of value.

Tinea corporis consists of scaly patches—round and erythematous. A noteworthy feature is that the patch spreads towards the periphery which is quite inflamed

while it tends to clear at the center. Local use of Whitfield ointment suffices. In case of poor response, it should be combined with griseofulvin.

Tinea cruris consists of similar lesions as in tinea corporis. It is, however, limited to the genitocrural area, usually sparing the scrotum. Whitfield ointment brings about cure. **Tinea pedis** is the infection of the intertriginous area (between the toes) in the form of fissures and macerations or the plantar surface of the feet in the form of vesicular patches. Whitfield's ointment gives gratifying results.

Ringworm infection of nails (Fig. 36.6), also called **onychomycosis** is a rather more chronic and resistant condition. Griseofulvin treatment is good enough, but it has got to be administered for a prolonged period. Generally, finger-nails require 3–4 months and toe-nails 6–12 month's course. Some patients may have to be supplemented with topical antifungal applications.

Tinea versicolor (Pityriasis) is a common fungal infection of the skin in tropical regions. The etiologic fungus



Fig. 36.5: Alopecia. The cause was a fungal infection (*Tinea capitis*). The condition needs to be differentiated from traumatic alopecia, trichotillomania and alopecia areata.



Fig. 36.6: Ringworm infection of nails.



Fig. 36.7: Pityriasis. Tinea versicolor infection causes small yellowish-brown macules which slowly blend to form large disfiguring areas.

is the *Microsporum furfur*. The characteristic lesions are small yellowish-brown macules. These slowly blend to form large disfiguring areas. Concomitant hypopigmentation is usual. The common sites are chest, neck and back of trunk (Fig. 36.7).

Treatment is local application of 10% sodium thiosulfate twice daily. Whitfield ointment, 0.25–0.5% strength and selenium sulfide are also effective. Recurrences are frequent, however.

MONILIASIS (Candidiasis)

It is caused by the fungus, *Candida albicans* and is common in early infancy. The lesion may be scaly, papulovesicular or erythematous with sharp border. The common sites of involvement are diaper area, especially external genitalia (Fig. 36.8) and surrounding skin, inguinal region, axilla and other moist areas that are subject to rubbing. Besides skin, candidiasis may involve mucous membrane of the mouth (thrush) and even viscera.



Fig. 36.8: Vulval moniliasis. It needs to be differentiated from napkin rash and skin lesions of acrodermatitis enteropathica.



Fig. 36.9: Diaper rash. Note the erythematous rash over external genitalia and thighs as a result of pronged contact with urine and stools.

The causes include infection of the infant from mother's vagina. Broad spectrum antibiotics, diabetes, obesity, hypoparathyroidism, malnutrition, prematurity and adrenal insufficiency predispose to moniliasis.

Treatment consists of local application of 0.5% gentian violet, nystatin cream, iodochlorhydroxyquin or 3% amphotericin B.

DIAPER RASH (Nappie or Napkin Flash, Intertrigo)

This condition usually occurs sometime during the diaper-wearing period of infancy. It is attributed to excessive water-logging of the local skin from stools, urine and increased perspiration with retention of sweat. It is said to be a sort of reaction to ammonia formed in the voided urine.

Clinical Features

The rash may be mild erythematous reaction covering the perineal region, buttocks and genitalia (Fig. 36.9). In others, it may be severe with papulovesicular lesions and ulcers. Superadded infection with a fungus or bacteria may further complicate the picture.

Treatment

Once the diaper rash has occurred, treatment consists of exposing the affected area to warm, dry air during day time. At night, zinc oxide ointment may be applied locally. Superadded infections should also receive attention. If these measures prove ineffective, topical hydrocortisone (0.5–1%) application is indicated provided that candida infection has been excluded. Diaper care is of primary importance as regards prevention of this common problem.

PRICKLY HEAT (Sudamina, Heat Rash, Milia rubra)

This condition consists of pinhead sized erythematous papules over face, neck, shoulders and other areas where sweat glands are in plenty. The basic lesion is obstruction of openings of sweat glands from excessive sweating. The most common cause is hot weather or overclothing. It may occur in febrile illnesses. Treatment is directed at reducing too much of clothing and providing cool and dry environment. A good quality dusting powder or calamine lotion is of value.



Fig. 36.10: Seborrheic dermatitis. Note the diffuse scaling and crusting of the scalp (cradle cap) and erythematous rash over the face.

SEBORRHEA

Seborrheic dermatitis, a disease of unknown etiology, is very common in infancy and childhood. Usually, it fails to receive attention in the wake of more dramatic picture of the major illness.

Clinical Features

Dandruff or seborrhea of the scalp is characterized by scaling and poorly circumscribed erythematous rash covered with oily crusts (Fig. 36.10). **Cradle cap** is the name given to it in case of infants. This may extend downward to involve all the oily areas such as forehead, neck, ears, eyebrows and nose.

Treatment

Seborrheic dermatitis of scalp responds well to a local application containing salicylic acid, sulfur and coal tar. Among other antiseborrheic agents, selenium sulfide suspension is of outstanding value. For seborrhea of face and rest of the body, 1% hydrocortisone (or other steroid cream) or iodochlorhydroxyquin is effective. Hydrocortisone application is indicated in resistant cradle cap too. Along with these measures, child's nutrition should be taken care of and vitamin supplements given if needed. Also, fat should be reduced in diet and any influences causing tension avoided.

URTICARIA

(Nettle Rash)

A common, but self-limiting disorder, it is allergic in origin. The characteristic lesions are very irritating wheals that may blend to involve large areas of the body (Fig. 36.11). Rash is frequently noticed, after a warm bath, around pressure points of the body.

A localized form of urticaria is called **angioneurotic edema**. It may involve lip or some other part of face, penis or larynx. The swelling is usually over in a matter of hours. Treatment consists of local application of calamine lotion



Fig. 36.11: Urticaria (nettle rash).

and antihistaminic agents to relieve itching. If unsuccessful, epinephrine or corticosteroids may be employed.

PYODERMAS

The skin of infants and young children is particularly susceptible to infections with *Staphylococcus* and *Streptococcus*. Skin response to such a bacterial pathogen is dramatic in the form of blisters. *Why?* Perhaps, because of its immaturity or some biochemical and other factors.

Classification

- Primary
 - Dermatitis exfoliative of newborn
 - Impetigo (Fig. 36.12)
 - Folliculitis (furuncles)
 - Sweat gland infections



Fig. 36.12: Impetigo. Note that the vesicular and pustular lesions are covered by thick crust. Pain and systemic manifestations are usually conspicuous by their absence. Itching, lymphangitis and regional lymphadenitis are common. Penicillin is the drug of choice for this superficial skin infection due to group A beta-hemolytic streptococci.

Box 36.2**Complications of bacterial skin infection (pyodermas)**

- **Uninhibited spread:** Cellulitis, osteomyelitis, septic arthritis, pneumonia, cavernous sinus thrombosis
 - **Acute streptococcal:** Scarlet fever, lymphangitis, lymphadenitis
 - **Post streptococcal:** Acute glomerulonephritis.
- Paronychia infections.
- **Secondary:** Superadded on conditions like:
- Scabies
 - Seborrhea
 - Diaper rash.

Treatment

Local applications of an ointment containing neomycin and bacitracin together with oral or systemic penicillin, erythromycin, cloxacillin or cephalexin are the treatment of choice. In mild infections, gentian violet, 0.5–1.0%, serves the purpose. Untreated pyoderma may be complicated by several conditions (Box 36.2).

Recurrent pyodermas warrant use of a soap substitute containing hexachlorophene followed by rinsing of the head by all family members with 70% alcohol regularly. This is in addition to the treatment outlined for acute infection. Attention to hygienic aspects is also essential to prevent recurrences.

ERYSIPELAS

This streptococcal skin infection is characterized by cellulitis and lymphangitis only of the skin (subcutaneous tissue is spared). Manifestations include large patch of erythema with induration and raised firm borders, pyrexia and irritability. As erythema stops progressing marginally, constitutional symptoms disappear (Fig. 36.13).

Complications include deep cellulitis, subcutaneous abscess formation and septicemia with metastatic abscesses/foci. Drug of choice is penicillin.

SCALDED SKIN SYNDROME (SSS)

Also termed **Ritter disease**, **Lyell syndrome** or **toxic epidermal necrolysis**, this condition may be the result of *Staphy-*



Fig. 36.13: Erysipelas. Note a large erythematous patch with induration. It is a superficial cellulitis involving the skin only. Subcutaneous tissue is spared.



Fig. 36.14: Staphylococcal scalded skin syndrome (SSSS). Nikolsky sign (separation of areas of epidermis in response to gentle stroking) was positive.

lococcus aureus infection, drugs (aspirin, allopurinol, phenobarbital, methotrexate, penicillins, phenyl-butazone, diphenylhydantoin, sulfas, thiazides) or immunologic disturbance (graft-vs-host disease).

Staphylococcal scalded skin syndrome (SSSS) is the one most frequently seen in clinical practice. It is a generalized manifestation of a local *staphylococcus aureus* infection, usually phage 2 type, the initial infective focus being in the umbilicus, circumcision site, conjunctiva or oropharynx. The infecting strains of the staphylococci elaborate an exotoxin, exfoliatin, which is responsible for the clinical manifestations.

The clinical picture is characterized by appearance of a generalized rash which is followed by development of superficial bullae filled with clear nonsterile fluid. The bullae have a tendency to rupture easily. Desquamation of extensive areas of epidermis occurs, leaving raw, weeping, red scalded looking surface, initially in the flexures and later over most of the body. At this stage, light rubbing or stroking of the skin results in wrinkling and separation of the outer layers of the epidermis, the so-called **Nikolsky sign** (Fig. 36.14). Healing of the lesions occurs rapidly and is complete in 1–2 weeks without leaving any scarring.

Accompanying manifestations include superficial stomatitis, conjunctivitis or pharyngitis. Complications include dehydration, electrolyte imbalance, cellulitis, pneumonia, septicemia and faulty temperature regulation. Therapeutic measures must include semi-synthetic penicillinase-resistant penicillin, say cloxacillin.

ICHTHYOSIS*

This term refers to hereditary hyperkeratinization (excessive cornification) of skin which becomes dry, thick and scaly.

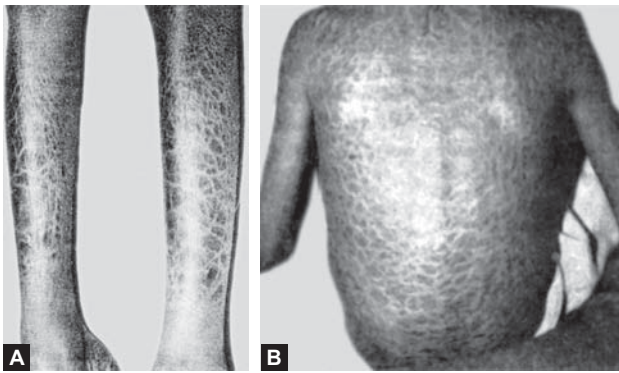
X-linked ichthyosis, a relatively common condition, is seen in males only. It manifests right at birth, or by the age of 4 months. There is frequent involvement of scalp and neck besides limb and trunk. The palms and soles are spared. There is no hair and nail involvement. Corneal

* Drugs like triparanol and diseases like malnutrition, malabsorption state, hypothyroidism or Hodgkin lymphoma may cause ichthyosis-like picture.

712 opacities may be seen in patients and carrier mothers and sisters. There is a seasonal variation in intensity. The cause is deficiency of steroid sulfatase (a microsomal enzyme) activity in skin fibroblasts. It is interesting that most mothers of such patients have history of failure to go into labor spontaneously and were refractory to the agents usually employed to induce parturition.

Ichthyosis congenita is characterized by a thick horny covering, with intervening prominent fissures, of a very remarkable severity. **Ichthyosis vulgaris** is characterized by slight scaling and dryness, mostly over arms and legs, which is worse during winter months. Its severe form is characterized by widespread scaling, geometrical figures separated by shallow fissures (Figs 36.15A and B). Follicular hyperkeratosis or palmoplantar lesions occur frequently. Inheritance is autosomal dominant. It should be differentiated from secondary ichthyosis (Fig. 36.16) which disappears following treatment of the causative factor.

Congenital ichthyosiform erythroderma is characterized by widespread hyperkeratosis and persistent erythema. The



Figs 36.15A and B: Ichthyosis vulgaris. (A) Extensive scaling over extensor aspects of legs giving appearance of varied geometrical figures; (B) Widespread scaling giving appearance of geometrical figures, over the back.



Fig. 36.16: Secondary ichthyosis. Note the classical lesions. Following antituberculous therapy (note the massive cervical adenitis) and improvement in nutritional status, skin lesions disappeared.



Fig. 36.17: Lamellar ichthyosis. Note that the collodion membrane is in the process of desquamation.

skin lesions improve, but intolerance to heat during summer months is troublesome. In a newborn, it manifests as blisters, ectropion and claw-like fingers. Lamellar exfoliation of newborn is characterized by a widespread keratinous covering which starts peeling off within 24 hours leaving normal underlying skin. The process of peeling is over in a few months.

Collodion baby, usually a form of lamellar ichthyosis, is characterized by a thick membrane at birth, flattened nose and ears, ectropion and lips fixed in an "O-like" configuration. The membrane sheds, the process taking a week to several weeks (Fig. 36.17). High susceptibility to skin infections has a bearing on the eventual outcome.

Harlequin fetus, a very rare autosomal recessive disorder, is characterized by thick, horny membrane over the whole body, grotesque appearance with flattened nose and ears, gross ectropion, chemosis, everted and gaping lips, absent hair and nails, restricted mobility of joints, poor suckling and respiratory difficulty. Prognosis is bad, a vast majority of patients dying in the first few weeks.

When present in association with cerebellar ataxia, progressive nerve deafness, polyneuritis and retinitis pigmentosa, ichthyosis is called Refsum syndrome. It usually manifests after 4 years of age. Association of ichthyosis with keratitis and neurosensory deafness is termed **Keratitis-ichthyosis-deafness (KID) syndrome**.

There is no specific treatment. The recommendations include lubrication of skin with emollients and keratolytic agents, say mineral oil and/or topical vitamin A and large doses of vitamin A (oral) and salicylic acid or retinoic acid in winter.

CAFE AU LAIT SPOTS

Cafe au lait spots are brownish, oval macules, found anywhere on the body in 22% of dark and 10% of white children (Fig. 36.18). The presence of six or more such spots of the diameter more than 0.5 cm in prepubescent and 1.5 cm in



Fig. 36.18: Café au lait spot. Note the (>2 cm diameter) dark macule this may be a normal finding in many children. More than six such spots point to neurofibromatosis or pseudohypoparathyroidism. Also seen is a fistula tract of a drained abscess over gluteal region.

postpubescent subjects should arouse suspicion of neurofibromatosis or Albright syndrome (pseudohypoparathyroidism).

ALBINISM

Albinism is an inborn error of metabolism, characterized by poor or nil pigmentation of the skin and hair (Fig. 36.19). In total albinism, iris is pink or bluish and pupils are red. Photophobia, nystagmus and refractive errors are common. Incidence of mental retardation among albinos is high. Genetically speaking, albinism is an autosomal recessive disorder. Consanguinity can be traced in a large proportion of the cases.

The basic defect is the deficiency of the enzyme, tyrosinase. The particular enzyme is responsible for conversion of dihydroxyphenylalanine (DOPA) to melanin. No specific treatment is available for this condition. However, refractive errors should be corrected. Further, eyes and skin should be protected from the bright sunlight.

VITILIGO

(Leukoderma)

This genetic disorder is characterized by milk white patchy lesions over skin (Fig. 36.20). The cause is an autoimmune damage to melanocytes in the dermis. Treatment is in the form of local steroid application and systemic psoralens. Prognosis is guarded. Hypopigmented (light rather than white) and anesthetic macules may well be a manifestation of leprosy. For details, refer to Chapter 19 (Bacterial Infections).

LEPROSY

(Hansen Disease)

Leprosy, caused by *Mycobacterium leprae*, is a chronic granulomatous disease characterized by hypopigmented skin lesions and/or sensory loss from involvement of the nerves.

India is responsible for 25% of the 12 million total cases of leprosy in the world. In the north Indian states, its incidence is far less than in the rest of the country. Unlike



Fig. 36.19: Albinism (left) against a control (right). The patient suffered from marked photophobia. He had juvenile diabetes too.



Fig. 36.20: Vitiligo. Note the completely depigmented macules of varying shapes and sizes.

adults, early manifestations of leprosy in childhood are often misleading. Generally, it is not diagnosed until the age of 4–5 years though the child may have been infected much earlier.

Etiopathogenesis

Leprosy is caused by *Mycobacterium leprae*. The source of infection is a patient, either from the family or from the community.

In a large majority, infection occurs either from bacteria containing discharge from the open skin lesions or from ulcers in nose, mouth, etc. Recently, it has been demonstrated that infection can occur from the bacilli in the breast milk. The most important portal of entry for the would-be host is a cut or abrasion in skin. Direct contact is not essential. Indirect contact through infected objects can also cause transmission of infection. It has been suggested that infection *via* respiratory or gastrointestinal tract (GIT) is also possible.



Fig. 36.21: Lepromatous leprosy: Hypopigmented skin patch with definite loss of sensation in an adolescent. The clinical diagnosis of leprosy was supported by acid-fast positive skin smear.

Clinical Classification/Features

Lepromatous Leprosy

In a typical case, body shows little resistance to the spread of bacilli which disseminate by billions, especially in subdermal and nervous tissues. In the nose, involvement of the cartilage may cause collapse of hard structures. Hair follicles are notably affected, causing loss of eyebrows. This, together with swelling of hands and feet, is a useful pointer to diagnosis.

In a classical severe case, skin appears thickened and greasy. Where the body attempts to localize the disease, painless nodules appear. The ears, nose, chin, elbows and knees are important examples of such sites. Occasionally, numerous small, pale flat macules with loss of sensation (Fig. 36.21) may be found. The nerves are usually invaded, but inflammatory symptoms are minimal in the early stages.

The skin smears are strongly positive, but lepromin test is negative. Allergic lepra reactions, particularly while on treatment with sulfones, constitute a characteristic feature. High fever, arthralgia, adenopathy, iridocyclitis, orchitis and erythema nodosum—the so-called **Arthus phenomenon**—are prominent among the various lepra reactions.

Tuberculoid Leprosy

Here, body shows well-developed resistance to invasion by the bacilli. The skin smears are negative. Lepromin reaction is strongly positive. The skin manifestations are characteristic. Macules are few and well-defined with raised margins and central healing. These are always anesthetic, except over the face.

The peripheral nerves are often involved at random in contrast to lepromatous type where polyneuritis is essentially distal and symmetrical. The ulnar, peroneal and great auricular nerves are most frequently involved, showing clinical enlargement with pain and anesthetic areas of skin. In addition, glove and stocking anesthesia of the hands and feet is a common feature. Trauma causes

secondary injuries, ulceration and infection. Contracture of the medial two fingers from ulnar involvement is a typical diagnostic sign.

Borderline Leprosy

Between the typical lepromatous tuberculoid cases are a large number of borderline cases with manifestations of both the types. This type, unlike the lepromatous and tuberculoid types, is immunologically unstable. If untreated, it can degenerate from borderline tuberculoid to borderline lepromatous.

Treatment may shift borderline lepromatous to borderline tuberculoid. This is frequently accompanied by acute neuritis and flaring up of skin lesions (reversal reaction).

Diagnosis

A punch biopsy from edge of the skin or nose lesion confirms the clinical diagnosis.

Treatment

The time-honored drug for treatment of leprosy continues to be dapsone or diaminodiphenyl sulfone (DDS). For dosage see Tables 36.2 and 36.3. Clofazimine (Lamprene) is a far better antileprosy drug. But it is also far more expensive than DDS. The dose is 100 mg twice daily for all ages.

The latest introduction in the antileprosy regimen is rifampicin which is safe and very effective. But it also costs exorbitant. It has been suggested that the patient may be given a single large dose of this drug to destroy the majority of the bacilli and then followed with maintenance dose of clofazimine/DDS.

Duration of treatment should be minimum of 7 years for lepromatous and borderline lepromatous, 5 years for borderline tuberculoid and 3 years for tuberculoid types. In the wake of appearance of multidrug resistant (MDR) strains, the World Health Organization (WHO) has

Table 36.2: Initial dose of diaminodiphenyl sulfone (DDS) to be given on alternate days

Weight range	Dose
Below 10 kg	10 mg
10–20 kg	25 mg
20–30 kg	50 mg
Beyond 30 kg	100 mg

Table 36.3: Maximum dose of diaminodiphenyl sulfone (DDS) to be given on alternate days

Stage of treatment	Dose
First month	5 mg
Second month	10 mg
Third month	25 mg
Fourth month	50 mg
Fifth month	100 mg

Table 36.4: WHO MDT in MDR leprosy (multibacillary)

Drugs	Dosage	
	6–9 years	10–14 years
Rifampicin (once a month, supervised)	300 mg	450 mg
Clofazimine (once a month, supervised)	100 mg	150 mg
Clofazimine (self-administered)	50 mg (daily or twice a week)	50 mg (daily or on alternate day)
Dapsone (once a month, supervised)	50 mg	50 mg
Dapsone (daily, self-administered)	25 mg	50 mg

Abbreviations: WHO, World Health Organization; MDT, multidrug therapy; MDR, multidrug resistant.

Table 36.5: WHO MDT in MDR leprosy (paucibacillary)

Drugs	Dosage	
	0–5 years	6–14 years
Rifampicin (once a month, supervised)	300 mg	450 mg
Dapsone (daily, self-administered)	25 mg	50 mg

Abbreviations: WHO, World Health Organization; MDT, multidrug therapy; MDR, multidrug resistant.

recommended the following combinations of multiple drugs:

- For **multibacillary leprosy**, 24 pulses of multiple drugs, each pulse administered over a period of one month (Table 36.4).
- For **paucibacillary leprosy**, the recommended regimen is 6 pulses of multidrug therapy (MDT), one every month (Table 36.5). Rehabilitation is a “must” in the presence of deformities.

Prevention

Bacillus Calmette–Guérin (BCG) vaccination is said to give some degree of protection. Maintenance of good nutrition and hygiene in children exposed to infected lepromatous or borderline lepromatous cases contributes to prevention. Whether they should be kept on prophylactic doses of DDS remains at present debatable.

HEMANGIOMA

It is an example of hematoma in which vascular tissue is present in excess in the skin. Three types are usually recognized—port wine stain or mark (nevus flammeus) is a well-defined flat, superficial non-blanching angiomas, red to dark purple in color, that may involve up to half of the body surface of the newborn, the back of the neck and face showing special predilection though any area of the body may be involved (Figs 36.22 and 36.23). It may accompany Sturge-Weber syndrome, Klippel-Trenaunay-



Fig. 36.22: Large hemangioma. Note that no other body part was involved.



Fig. 36.23: Extensive port wine stain (nevus flammeus).

Weber syndrome, Rubinstein-Taybi syndrome, Cobb syndrome, Beckwith syndrome and trisomy 13.

Capillary hemangioma (strawberry mark) is a sharply-demarcated, somewhat raised, semiblanching, bright red spot, which may be present at birth, but usually appears during the earlier weeks of life. The size varies from many mm to 2 or 3 cm. An overwhelming majority disappear spontaneously by 10 years of age. This type is the most common.

Cavernous hemangioma is a relatively uncommon vascular anomaly of large, sinus like blood vessels of skin. It appears as a raised, deep seated, poorly demarcated purple spot that blanches on pressure (Fig. 36.24). Like capillary type, cavernous hemangioma too disappears in most cases in early childhood. This hemangioma may lead to hypertrophy of the involved limb.

Usually no treatment is required. If, however, a large hemangioma persists, it has got to be removed by carbon dioxide freezing, surgical excision and grafting, cryosurgery and tattooing. Laser therapy, now emerging as the modality of choice, may be resorted to. Some cavernous hemangiomas may respond to a course of steroids followed by compression.



Fig. 36.24: Massive cavernous hemangioma.

The complications in capillary or cavernous hemangioma include superimposed infection, trauma, and ulceration, bleeding due to thrombocytopenia and rarely disseminated intravascular coagulation (DIC). In some instances, arteriovenous fistulae may occur.

TELANGIECTATIC ANGIOMA (Spider Nevus)

It consists of a central dilated capillary with many radiating vessels and is most often found over the face (Fig. 36.25). Two types are known:

1. **Hereditary** (Osler-Weber-Rendu disease) in which mucus membrane lesions occur early in life followed later by skin lesions. GIT bleeding may occur.
2. **Acquired** as in cirrhosis.

Treatment is freezing with liquid nitrogen or carbon dioxide, or diathermy electrocoagulation of the central area.

EPIDERMOLYSIS BULLOSA (EB)

This group of conditions is characterized by congenital blistering precipitated by mechanical irritation and high environmental temperature.



Fig. 36.25: Telangiectatic angioma. The lesion seen here, responding to blanching, were seen in child with cirrhosis.

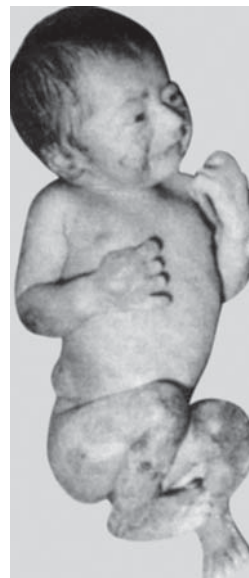


Fig. 36.26: Epidermolysis bullosa.

- **Epidermolytic EB** is an autosomal nonscarring form in which blisters may be present right at birth or in neonatal period (simplex type) (Fig. 36.26), or appear after first year of life especially over feet and hands (Weber-Cockayne type).
- **Junctional EB** also nonscarring, may be of milder autosomal recessive type (generalized atrophic type) or with life-threatening complications (letalis or herlitz type)
- **Dermolytic EB** is characterized by scarring and may be of two types—(1) dominant dystrophic in which, besides rapidly healing blisters, involvement of nails is common and in some even mucus membrane may be affected, (2) recessive dystrophic in which mucus membrane lesions are common, leading to nutritional deprivation; deformities of hands and feet may occur. Affected children must be protected against mechanical trauma and heat and superimposed infection and undernutrition. Genetic counseling is indicated.

ERYTHEMA MULTIFORME

The term refers to a disorder characterized by series of concentric circles. Corresponding to vasodilatation, edema and oozing of red cells, each circle is red, white and blue from outside to inside. Associated lesions may include pruritic erythematous half circles, polycyclic erythema, urticaria, bullae and erosions (Fig. 36.27). A severe bullous type involving skin, eyes, genitalia and mouth and with severe systemic manifestations is called **Stevens-Johnson syndrome (SJS)** (Figs 36.28 and 36.29).

A wide variety of etiologic factors such as viruses, bacteria, fungi, vaccination and drugs (especially sulfas) have been implicated. Treatment in simple erythema multiforme is removal of the offending agent, oral antihistaminic, agents, cool compresses and wet dressing. SJS is an indication for parenteral nutrition and administration of antibiotic(s) and steroids.



Fig. 36.27: Erythema multiforme minor. Note the symmetrical crops of skin lesions of diverse morphology with relative sparing of the mucous membranes.



Fig. 36.28: Erythema multiforme major (Stevens-Johnson syndrome). Note extensive involvement of the skin and mucous membranes, including purulent conjunctivitis and uveitis, as also toxic appearance.



Fig. 36.29: Stevens-Johnson syndrome. Note the healing skin and mucous membrane lesions during recovery.

PEMPHIGUS

Pemphigus vulgaris is characterized by painful ulceration in the buccal cavity followed by large bullae (deep in the epidermis) over trunk and head. On slight pressure, avulsion of the epidermis occurs. This is called **Nikolsky sign**. The lesions rupture, leaving behind raw area which shows little inclination to heal (Fig. 36.30).

Pemphigus foliaceus is characterized by rather superficial blisters (high in the epidermis) which tend to rupture quickly, leaving behind crusts and scales. Scalp, face, neck and upper trunk are the common sites. Unlike pemphigus vulgaris, it is a relatively benign condition. Treatment is with systemic steroids. Pemphigus vulgaris may need cyclophosphamide, azathioprine or gold salts for maintenance of the remission achieved with steroids.

EHLER-DANLOS SYNDROME

This genetic connective tissue disorder is characterized by hyperelasticity (Fig. 36.31), fragility and easy bruising (Fig. 36.32) of the skin. Marked fragility of the skin is responsible for minor trauma resulting in ecchymosis, bleeding and poor healing. Atrophic cigarette-paper scars over pressure points, legs and forehead are suggestive of the diagnosis (Figs 36.33A and B).

At least ten forms of the syndrome have been described. No specific treatment is yet available. Nevertheless, life expectancy is, as a rule, normal. A major complication like rupture of lung, bowel or great blood vessels may prove fatal. Remaining complications include skeletal deformities and ocular defects.

MOLLUSCUM CONTAGIOSUM

It is a contagious and autoinoculable skin disease caused by the largest virus (poxvirus) and is characterized by multiple small white or pink tumor-like masses (pinhead to pea size) on face, neck (Fig. 36.34) trunk and intertriginous areas.



Fig. 36.30: Pemphigus. Note the large bullae, deep in the dermis, which, together with the oral ulceration, suggest "pemphigus vulgaris".



Fig. 36.31: Ehler-Danlos syndrome. Hypermobile joints.



Fig. 36.32: Ehler-Danlos syndrome: Easy bruising.



Figs 36.33A and B: Classical cigarette-paper scars in two subjects with Ehler-Danlos syndrome.



Fig. 36.34: Moluscum contagiosum. Note the well-circumscribed and umbilicated papules.

Source: CDC, Centers for disease control and prevention

The well-circumscribed and umbilicated papules need to be differentiated from warts. Treatment, in cases who fail to have spontaneous resolution in 6–9 months, is removal by curettage. It consists of expressing the cheese-like material with forceps followed by application of tincture iodine or carbolic acid. Liquid nitrogen therapy, electrocautery, cryotherapy and laser therapy too are available. Mild disease may respond to application of cantharadine, podophyllotoxin or trichloroacetic acid.

WARTS

This contagious disease is caused by human papilloma virus (HPV) and is characterized by verrucose papules (common warts, verruca vulgaris) or flat lesions (plane warts) on anogenital region or elsewhere, say soles and subungual region.

If spontaneous resolution fails to occur in several months, treatment is local application of cantharid in or a keratolytic agent such as salicylic acid for 2–3 months or a physical

removal by curettage, electrocautery, chemical cautery, cryotherapy and laser therapy. An expensive therapy in the form locally injectable interferon alfa too is available.

ERYTHEMA NODOSUM

The condition is characterized by appearance of painful erythematous (bright red) nodules on the shins (Fig. 36.35). Occasionally there is involvement of forearms and rarely of calves, thighs and soles. At a time, not more than four nodules may be seen. The lesions fade in a week or two, leaving behind a brownish discoloration.

The condition is an allergic vasculitis and may be associated with tuberculosis, streptococcal sensitivity as in rheumatic fever, ulcerative colitis, Crohn disease, sulfonamide therapy, histoplasmosis and coccidiomycosis. Treatment consists of giving bed-rest until all the lesions have subsided application of topical steroid cream, oral steroids and removal of the offending agent or eradication of the underlying disease.



Fig. 36.35: Erythema nodosum.

SKIN TUBERCULOSIS

It is described in Chapter 26 (Pediatric Pulmonology).

ECTODERMAL DYSPLASIAS

These are a group of conditions characterized by dominant involvement of ectodermal structures, e.g. skin, teeth, hair, nails and endocrine and sebaceous glands.

Anhidrotic type, the most common, is usually X-linked recessive though autosomal recessive inheritance may also occur. The triad of lack of or poor sweating (anhidrosis or hypohidrosis), anomalous dentition (usually widely-spaced peg-shaped teeth) and sparse hair (hypotrichosis) is characteristic of this type (Figs 36.36 to 36.38). Episodes of unexplained pyrexia are common.

Hydrotic (Clouston) type is manifested by hyperkeratosis of palms and soles, dystrophic nails and sparse hair. Sweating is normal. Dentition is usually not affected.

Robin type, an autosomal dominant disorder, is characterized by dystrophic nails, peg-shaped teeth and sensorineural deafness. **Rapp-Hodgkin type**, an autosomal dominant disorder, manifests with poor sweating, dystrophic nails, sparse hair, oral clefts, hypospadias and growth retardation.



Fig. 36.36: Anhidrotic ectodermal dysplasia. Note the sparse scalp hair.



Fig. 36.37: Anhidrotic ectodermal dysplasia. Note the peg-shaped incisors.



Fig. 36.38: Anhidrotic ectodermal dysplasia.

EEC syndrome, an autosomal dominant disorder, consists of ectodermal dysplasia (thin, dry skin, sparse hair, dystrophic nails), ectodactyly, cleft lip and palate.

ACNE

Acne is a subacute or chronic inflammatory disorder characterized by appearance of pleomorphic lesions usually over the face and the trunk though, occasionally, arms, legs and buttocks may also be involved. Several varieties of acne are recognized, namely acne vulgaris, infantile acne, steroid acne, halogen acne, tropical acne and acne conglobata.

- **Acne vulgaris**, a sort of physiologic event occurring universally in adolescence with a slightly greater preponderance in males, is characterized by four basic types of lesions, i.e., early whiteheads or blackheads called **comedones** (Fig. 36.39), papules, pustules and nodulocystic lesions with interspersed scarring. The lesions are usually confined to the face with predominance over the forehead (the so-called **promade acne** due to application of petroleum jelly or other greasy



Fig. 36.39: Acne vulgaris.

hair preparations). At times chest, upper back and deltoid areas are also involved.

A functional mature sebaceous gland that enlarges and produces excessive sebum in response to increased activity of androgens during adolescence is the seat of acne lesions. Colonization with organisms, propionibacterium acnes, *Staphylococcus epidermidis* and perhaps, *Pityrosporon ovale*, sets up an inflammatory reaction in the comedone.

Treatment consists of clarifying to the adolescent as well as the parents that frequent cleansing, cosmetics, hair preparations and facial manipulations are harmful and must be avoided. Among the topical preparations, benzoyl peroxide gels and retinoic acid (which reduce the Propionibacterium acnes count and number of visible comedones) are most effective though sulfur, salicylic acid and resorcinol are also useful and acceptable for mild keratolytic effect.

Recommended topical antibiotics for infected comedones include clindamycin, erythromycin and tetracycline. Topical therapy needs to be given for several weeks for perceptible outcome. Together with topical therapy, systemic administration of erythromycin, tetracycline or some other suitable antibiotic is recommended for better results.

Physical therapy includes ultraviolet light (natural sunlight suffices), CO₂ snow or slush. Surgical therapy revolves round extraction of open and closed comedones, needle aspiration of nodulocystic lesions, steroid injection into acne cysts and dermabrasion to safeguard against scarring.

- **Chlor acne** results secondary to halogenated aromatic hydrocarbons (direct contact, inhalation or ingestion). The lesions are predominantly comedonal and less frequently inflammatory (papules, pustules, nodules, cysts). Healing occurs by hypertrophic or atrophic scarring. Though antibiotics and benzyl peroxide are of little value, topical or oral retinoids are effective.
- **Neonatal acne**, occurring in 20% of neonates, is characterized by comedones predominantly on cheeks and forehead. It may be due to placental transfer of maternal androgens, hyperactive neonatal adrenal glands

and a hypersensitive neonatal endorgan response to androgenic hormones. It responds well to benzyl peroxide and tretinoin.

- **Infantile acne**, resembles acne vulgaris except that nodulocystic lesions are infrequent and scarring is absent, may occur in first month of life in male children in particular as a hypersensitivity end-organ response to hormones. The lesions are confined to face. One or both parents have had severe acne during their adolescence. Predisposition to severe acne is quite likely. Application of benzoyl peroxide or a mild acne lotion usually clears the lesions within a few weeks.
- **Steroid acne**, a sort of monomorphous folliculitis over the face, neck, chest, shoulders, upper back, arms and rarely, the scalp, follows 2 weeks after systemic or topical steroid therapy. Characteristically, erythematous papules or pustules in the same stage of development are seen. Comedones are infrequent and the nodulocystic lesions and scarring rare. Similar acne may occur in congenital adrenal hyperplasia as well. Application of retinoic acid and benzoyl peroxide gel is effective.
- **Halogen acne**, dominated by highly inflammatory lesions may follow administration of iodide or bromide-containing medications. Withdrawal of the medication with application of an anti-acne topical preparation regresses the lesions.
- **Tropical acne**, characterized by dominantly suppurating nodulocystic lesions over the back, chest and buttocks, with superadded infection, is secondary to intense heat and humidity. Elimination of environmental factors is an essential prerequisite for successful outcome with acne therapy.
- **Acne conglobata**, characterized by papules, pustules, nodules, cysts, abscesses, sinus tracts and severe scarring over body (relatively sparing the face) with constitutional symptoms and anemia, occurs in adolescents and adults. Since routine acne therapy is usually ineffective, these subjects need systemic steroids or sulfones to suppress inflammation, and isotretinoin. The last-named agent is known for its teratogenic adverse effects.
- **Acne fulminans** (acute febrile ulcerative acne) is characterized by an abrupt development of extensive inflammatory (ulcerative acneform) lesions over the chest and back of the adolescent boys. Accompanying the lesions are constitutional manifestations in the form of fever, arthralgia, myalgia, loss of weight, debilitation and leucocytosis. The lesions spare the face and heal by scarring. Treatment is with oral steroids, isotretinoin, dapsone and antibiotics in the presence of superadded infection.

PSORIASIS

Psoriasis, a disease of unknown etiology, unknown inheritance and unknown pathogenesis, may occur in some 1% of children, usually in 3–10 years age group with predominance of girls. Rarely, it may occur in neonates—initially involving the diaper area and later assuming a severe and recalcitrant form.



Fig. 36.40: Psoriasis. Note erythematous papules. At places, these show a tendency to coalesce to form plaques with irregular sharp borders.



Fig. 36.41: Psoriasis. Note that the lesions are in the process of healing.

Clinical Features

The classical lesions consist of red papules that coalesce to form plaques with sharply demarcated irregular margins and silvery scales (Figs 36.40 and 36.41). Pinpoint hemorrhage follows removal of the scales. This is called **Auspitz sign**. The lesions show a tendency to appear at the sites of trauma, the so-called **isomorphic** or **Koebner response**.

The lesions usually occur over scalp, knees, elbows, umbilicus and genitalia, and less often involve the face and nails. The lesion of the so-called **guttate psoriasis**, that may follow a streptococcal throat infection, viral infections, sunburn, and withdrawal of steroid therapy, are usually seen over trunk, face and proximal portions of extremities.

Diagnosis

Important diagnostic points are:

- Pitting of the nailplate.
- Auspitz sign pinpoint bleeding spots following removal of yellowish-white scale.
- Koebner/isomorphic response, i.e., appearance of fresh lesions at the site of trauma.

Treatment

Therapeutic measures include application of coal tar preparations, topical steroids, ultraviolet light/natural sunlight, psoralens and ultraviolet light (PUVA) and high doses of vitamin D. Treatment is by and large only palliative.

Multiple Choice Questions

1. Spot the wrong matching:

A. Purpura	A circumscribed lesion (from extravasation of blood) measuring less than 5 mm in diameter
B. Scar	A formation of connective tissue, that replaces the original/normal skin markings are absent
C. Poikiloderma	A triad of atrophy of skin, reticular pigmentation and telangiectasia
D. Patch	A macule larger than 1 cm in size
2. All of the following are major criteria of atopic dermatitis, except:
 - A. Pruritus
 - B. Distribution over face and convexities in infants under 2 years and over flexures in older children
 - C. Tendency to remain for short period
 - D. Personal or family history of atopy
3. An eruption characterized by a symmetrical itchy macule or papule which quickly spreads to the whole of the skin, including palms and soles and at times, the mucosal surface too is:
 - A. Drug eruption
 - B. SLE lesion
 - C. Insect bite
 - D. Scabies
4. Spot the wrong observation:
 - A. Infants and children with scabies may suffer from lesions over face, scalp and even over palms and soles may also occur
 - B. More than 6 café-au-lait spots, irrespective of size, suggest diagnosis of neurofibromatosis or pseudohypoparathyroidism

contd...

- C. Angioneurotic edema, a localized form of urticaria, is usually over in a matter of hours
 D. Most cases of scalded skin syndrome in pediatric practice are due to adverse drug reactions
5. A large erythematous patch with induration restricted to involvement of sheer skin is:
- Cellulitis
 - Erysipelas
 - Ecthyma
 - Impetigo

Answers

1. A 2. C 3. A 4. D 5. B

Clinical Problem-solving

Review 1

A 6-month-old infant, already on ampicillin plus cloxacillin for *Staphylococcal pneumonia*, has a sharply-demarcated, somewhat raised, semi-blanching, bright red spot measuring about 2.5 cm. According to parents, it was noticed when the child was 3 or 4 weeks old. The resident makes a diagnosis of cavernous hemangioma.

- Was the diagnosis made by the referring practitioner correct?
- What is the expected course?
- What treatment modalities are available?
- Any role of steroid and beta-blocker therapy?

Review 2

A 10-year-old girl, a known diabetic on insulin, presents with skin lesions comprising red papules coalescing to form plaques with sharply demarcated irregular margins and silvery scales. An attempt to remove the scales causes pinpoint hemorrhages. Furthermore, the lesions show a tendency to appear at the sites of trauma.

- What is the most likely diagnosis?
- What is the etiology of the condition?
- What is its treatment?

Answers**Review 1**

- No, it is unlikely to be cavernous hemangioma. The correct diagnosis should be capillary hemangioma (strawberry mark). This type is the most common among hemangiomas.
- An overwhelming majority disappear spontaneously by 10 years of age.
- Usually no treatment is required. A persistent large hemangioma may be removed by carbon dioxide freezing, surgical excision and grafting, cryosurgery and tattooing, or laser therapy, now emerging as the modality of choice, may be resorted to. Some cavernous hemangiomas may respond to a course of steroids followed by compression.
- Beta-blocker or steroid therapy may work for some cavernous hemangioma. There is evidence of its therapeutic role in capillary hemangioma.

Review 2

- This is a classical case of psoriasis. The lesions are typical of this disease. Two clinical signs, i.e. Auspitz sign (pinpoint hemorrhage on attempting to remove the scales) and Koebner response (tendency to appear at trauma site) lend support to this diagnosis.
- Etiology of psoriasis remains unknown. Even inheritance and pathogenesis are unknown.
- Therapeutic measures include application of coal tar preparations, topical steroids, ultraviolet light/natural sunlight, psoralens and ultraviolet light (PUVA) and high doses of vitamin D. Treatment is by and large only palliative.

FURTHER READING

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ACCIDENTAL POISONING: AN OVERVIEW

Accidental poisoning is an important cause of morbidity and mortality in childhood all over the world; the pattern and magnitude varies in different areas as also with changing times. Such mishaps are usually unintentional in children below 5 years with a peak occurrence around 18 months to 3 years due to exploratory behaviour, inability to discriminate safe versus unsafe agents and careless household storage of medicines and toxic substances like kerosene stored in water containers. Poisoning may be intentional and purposeful, may be with multiple agents and more common in girls than boys among children above 5 years and adolescents. Table 37.1 outlines the relative incidence of various accidental poisonings in hospitalized children India.

APPROACH

The principles of initial approach are:

- Resuscitation and stabilization
- History and physical examination
- Appropriate decontamination—gastrointestinal tract (GIT), skin and eyes
- Judicious use of laboratory tests, electrocardiography (ECG) and radiography
- Administration of specific antidotes
- Use of enhanced elimination techniques for selected toxins.

In the initial assessment, the attending doctor must rapidly decide whether a child is in a life threatening situation and standard airway, breathing and circulations (ABCs) of resuscitation is always the first priority. The first step should be to treat the patient and not the poison. The supportive measures are outlined in the Table 37.2. Next, take detailed history from the patient (if conscious), family members, friends or bystanders to identify the ingested substance, its amount, concentration, route, time elapsed and nature of any treatment administered.

Table 37.1: Relative incidence of accidental poisoning in hospitalized children in India

Poisoning	Incidence (%)
Hydrocarbon (kerosene)	50
Household medicines	20
Household substances (insecticides, pesticides etc.)	20
Miscellaneous	10

Table 37.2: Salient features of initial/supportive therapy in poisoning

Indications	Corrective measures
Airway obstruction and breathing difficulty	Keeping airway open by removing extraneous material, secretions. Bag and mask ventilation intubation, tracheostomy
Peripheral circulatory failure	Oxygen administration. Expansion of intravascular volume by suitable volume expander
Hypoglycemia	0.25 to 0.5 gm/kg 25% dextrose in water by IV push
Electrolyte imbalance	Appropriate fluid and electrolyte therapy
Cerebral edema	Mannitol
Seizures	Diazepam
Renal failure	Appropriate measures for ARF
Anemia, hemolysis	Blood Transfusion
Infection	Appropriate antibiotics

Abbreviations: ARF, acute renal failure; IV, intravenous.

Perform brief physical examination with particular attention to any specific odor in the breath/vomit and clothes, vital signs, sensorium (AVPU or Glasgow coma scale) and pupils. The positive findings of the physical examination may form a constellation of signs and symptoms referred to as toxidrome characteristic of exposure to a particular group of substances. Table 37.3 to 37.6 show common symptoms, signs and toxidromes of poisoning in children.

LABORATORY EVALUATION

No toxic panel is uniformly helpful.

- Electroencephalography (EEG) cardiac rhythm disturbances
- Chest X-ray (CXR) for aspiration pneumonia and pulmonary edema
- Serum electrolytes
- Arterial blood gas (ABG) estimations.

Certain medications may be seen on abdominal radiographs (Tables 37.7 and Box 37.1).

GASTROINTESTINAL DECONTAMINATION

Gastrointestinal (GI) decontamination aims at preventing absorption by gastric lavage, activated charcoal, cathartics and whole bowel irrigation. Syrup of ipecac induced emesis has no role in hospital setting.

Table 37.3: Examples of the vital sign changes commonly associated with various toxic agents

Temperature	
Hypothermia	Hyperthermia
<ul style="list-style-type: none"> Barbiturates Ethanol Narcotics Phenothiazines Sedative-hypnotics 	<ul style="list-style-type: none"> Anticholinergics Hallucinogens Monoamine oxidase (MAO) inhibitors Salicylates Sympathomimetics
Heart rate	
Bradycardia	Tachycardia
<ul style="list-style-type: none"> β-blockers Calcium channel blockers Clonidine Cyanide Digitalis Organophosphates 	<ul style="list-style-type: none"> Anticholinergics Ethanol Methylxanthines Sympathomimetics Cyclic antidepressants Sedative-hypnotics
Blood pressure	
Hypotension	Hypertension
<ul style="list-style-type: none"> Antihypertensives β-Blockers Calcium channel blockers Iron, narcotics Sedative-hypnotics 	<ul style="list-style-type: none"> Amphetamines Anticholinergic Phencyclidine Sympathomimetics Tricyclic antidepressants
Respiratory rate	
Hypoventilation	Hyperventilation
<ul style="list-style-type: none"> Clonidine Narcotics Organophosphates Sedative-hypnotics Cyclic antidepressants 	<ul style="list-style-type: none"> Methanol Carbon-monoxide Cyanide Methylxanthines Salicylates Sympathomimetics

Table 37.4: Examples of odors with various toxic agents

Odors	Toxic agents
Acetone	Acetylsalicylic acid
Garlic	Arsenic and organophosphate
Petroleum	Petroleum distillates

Table 37.5: Pupil changes associated with some toxins and drugs

Miosis (mnemonic COPS)	Mydriasis (mnemonic AAAS)
C—Cholinergics, Clonidine	A—Antihistamines
O—Opiates, Organophosphates	A—Antidepressants
P—Phenothiazines, Pilocarpine Pontine bleed	A—Anticholinergics, Atropine
S—Sedatives-hypnotics	S—Sympathomimetics (Cocaine, amphetamines)

Table 37.6: Toxidromes suggestive of different groups of poisoning agents

Toxins	Syndromes
Opioids	Respiratory failure, coma, miosis
Cyclic-antidepressants	Coma, seizures, dysrhythmias (QRS >0.10 sec)
Cholinergics (Organophosphates and carbamates)	Diarrhea, diaphoresis, urination, miosis bronchorrhea, bronchospasm, bradycardia emesis, lacrimation, salivation, vomiting fasciculations
Anticholinergics	Hyperthermia—hot as a hare
Atropine, phenothiazines antihistamines, mushrooms	Mydriasis—blind as a bat Dry skin and mucosae—dry as a bone Flushing—red as a beet. Delirium—mad as a hatter
Sympathomimetics	Mydriasis, anxiety, tachycardia, hypertension, hyperthermia, diaphoresis

Table 37.7: Laboratory tests that suggest poisoning

Abnormalities	Poisons
Hyperkalemia	Potassium, digoxin
Hypokalemia	Theophylline, barium, diuretics
Hypoglycemia	Insulin, salicylates, propranolol, oral hypoglycemic agents
Hyperglycemia	Salicylates (early stages), theophylline, iron
Hypocalcemia	Salicylates
Ketonuria	Salicylates

Box 37.1 Radio-opaque ingestants (mnemonic—CHIPS)

C—Chloral hydrate, chlorinated hydrocarbons
H—Heavy metals
I—Iron and iodides
P—Phenothiazine, potassium
S—Slow release capsules/tablets.

Box 37.2 Toxins poorly bound by activated charcoal (mnemonic—CHEMICLS)

C—Cyanide
H—Hydrocarbons
E—Ethanol
M—Metals
I—Iron
C—Caustics
L—Lithium
S—Solvents.

Gastric Lavage

It is indicated only if the patient arrives within one hour (golden hour) of ingestion, life threatening ingestions or for those substances that do not bind to charcoal (Box 37.2). Gastric lavage is done with large bore orogastric tube with 0.9% saline, 15 mL/kg (maximum 200–400 mL/cycle). It is contraindicated in caustic, hydrocarbon and sharps ingestion.

Activated Charcoal

It is a finely granular substance with a surface area of approximately 1000 m²/gm. Its microscopic pores permit adsorption of drugs and other large molecular weight substances. Maximum adsorption of charcoal to toxin occurs when the charcoal to drug ratio is 10:1. Because of its effectiveness both in enhancement of preabsorptive and postabsorptive elimination, only modest benefit of gastric emptying and cathartic administration, charcoal has become the single most first line treatment for significant toxic ingestions.

It should be administered in a dose of 1 gm/kg (maximum 50–60 gm). When repetitive doses are required, it can be given in this dose every 4 hourly (or 0.5 gm/kg every 2 hours). Prepare activated charcoal by mixing aqueous solution or its desiccated form with ice and add flavoring (cola or cherry syrup) if desired. Child can drink it from cup with a straw or instilled through orogastric tube. It is contraindicated in hydrocarbons, corrosive poisoning and in paralytic ileus.

Hyperosmolar adjunctive cathartics (sorbitol 70%) 0.5 gm/kg, 10–20 mL in children and 60–100 mL in adolescents, decrease the transit time, but are contraindicated in children below 6 years because of potential risk of fluid and electrolyte imbalance.

Whole Bowel Irrigation (WBI)

It decontaminates the entire gut and is indicated for ingestants not bound to activated charcoal, e.g. iron and slow-release drug preparations. WBI is accomplished through rapid administration of polyethylene glycol electrolyte lavage solution via nasogastric tube at a rate of 500 mL/hour in preschoolers and 1–2 liters/hr for teenagers. The end point is a clear rectal effluent. This procedure is contraindicated in patients with ileus, obstruction, perforation or significant GI hemorrhage.

Table 37.8: Indications of toxic elimination

Mode of elimination	Situation
Urinary alkalization	Significant salicylate and phenobarbital poisoning
Neutral diuresis by administration of excess intravenous crystalloids with contraindications of pulmonary and cerebral edema and renal failure.	Significant lithium or bromide poisoning
Hemodialysis	Methanol, ethylene glycol, significant salicylate, phenobarbital, theophylline and lithium poisonings

TOXIN ELIMINATION (ENHANCEMENT OF EXCRETION)

Several techniques are employed like urinary alkalization (iron-trapping) hemodialysis, peritoneal dialysis, hemoperfusion, exchange transfusion, plasmapheresis and drug antibodies (digoxin fab antibodies). These techniques are indicated only in a few situations (Table 37.8).

In theory, acidification and alkalization of urine enhance the excretion of weak bases and acids. The acidification should be avoided altogether because of the risks of acidemia and exacerbation of rhabdomyolysis. Charcoal hemoperfusion is rarely indicated and used most often in significant theophylline poisoning.

Administration of Antidotes

Antidotes and antagonists are available for only a minority of poisonings and should not be used indiscriminately. Overuse may complicate initial presentation by producing other forms of poisoning. Moreover the basic supportive care saves more lives than all the antidotes put together. Specific antidotes are listed in Table 37.9.

Table 37.9: Antidotes used in toxicology

Toxins/poisons	Antidotes	Dosages
Anticholinergics	Physostigmine	0.02–0.06 mg/kg upto 0.5 mg slowly IV/IM/SC repeated at 5 minutes interval until desired effect (max 2 mg)
Acetaminophen	N-Acetylcysteine	140 mg/kg PO or IV stat, Followed by 70 mg/kg × 17 doses (4 hrly)
Carbon monoxide	Oxygen	100% by tight fitting mask or hyperbaric oxygen
Cyanide	Sodium nitrite Sodium thiosulfate	0.33 mL/kg of 3% IV 1.65 mL/kg of 25% IV
Digoxin	Digoxin-specific antibodies (Fab) fragments (Digibind each vial binds approx 0.6 mg of Digoxin)	Children less than 20 kg, 1 vial (total amount ingested in mg ÷ 0.6 = No. of vials)
β-blockers	Isoproterenol dopamine, epinephrine	Infusion, titrate to effect
Iron salts	Desferroxamine (Desferal 500 mg/vial)	15 mg/kg/hr IV until urine color turns normal or iron level <100 µg/dL
Methemoglobin producing agents	Methylene-blue (10 mg/ampoule)	1–2 mg/kg IV (0.1–0.2 mL/kg 1% solution over 5–10 minutes may repeat after 4 hours.
Narcotics	Naloxone	0.1 mg/kg IV (max 2 mg). Repeat every 2–3 minutes till the reversal or cumulating dose of 10 mg.

contd...

Toxins/poisons	Antidotes	Dosages
Organophosphates	Atropine, pralidoxime	0.05 mg/kg IV every 10–30 min to achieve atropinization 25–50 mg/kg IV or IM as 5% solution 12 hours apart (if to be repeated)
Phenothiazines INH	Diphenhydramine (Benadryl), Pyridoxine	0.5–1 mg/kg IV/IM (max 50 mg), may be repeated every 30 minutes 1 mg/1 mg of INH ingested/(max IV 500 mg)

Abbreviations: IM, intramuscular; IV, intravenous; SC, subcutaneously; INH, isoniazid; PO, orally.

Prevention

The parents need to ensure that;

- All medicines and chemicals are kept beyond the reach of children, preferably under lock and key.
- Drugs and medicines are dispensed in their original containers and administered under direct supervision and not without specific written prescription of the doctor.
- Potential household substances like kerosene, other petroleum distillates, insecticides, pesticides are kept in their original containers and not transferred to empty containers used for food stuffs and must be labeled as **Poison** prominently.
- Infants and toddlers should not be left unattended.
- Parents should also be educated not to panic in case of ingestion of some nontoxic household substances (Box 37.3).
- There is need to establish Poison Control Centers in each state/district in order to compile and disseminate information on management and promote research in this field.

Box 37.3 Nontoxic household products

- Shaving cream, shampoo
- Ballpoint ink
- Bubble bath soaps
- Birth control pills
- Candle
- Cosmetics, powders
- Chalk
- Cigarettes
- Crayons
- Toothpaste
- Deodorants
- Lipstick
- Mosquito repellants
- Pencil (Graphite)
- Matchesbox
- Saccharin
- Water colors
- Incense.

HYDROCARBON POISONING

- Poisoning from hydrocarbons depends on their viscosity, volatility and surface area.
- Examples of hydrocarbons with low viscosity and low volatility are kerosene, turpentine, polish employed for furniture. These have higher risk of aspiration.
- Examples of low viscosity, but high volatility are gasoline, naphtha, benzylene derivatives like toluene. These have higher risk of CNS toxicity.

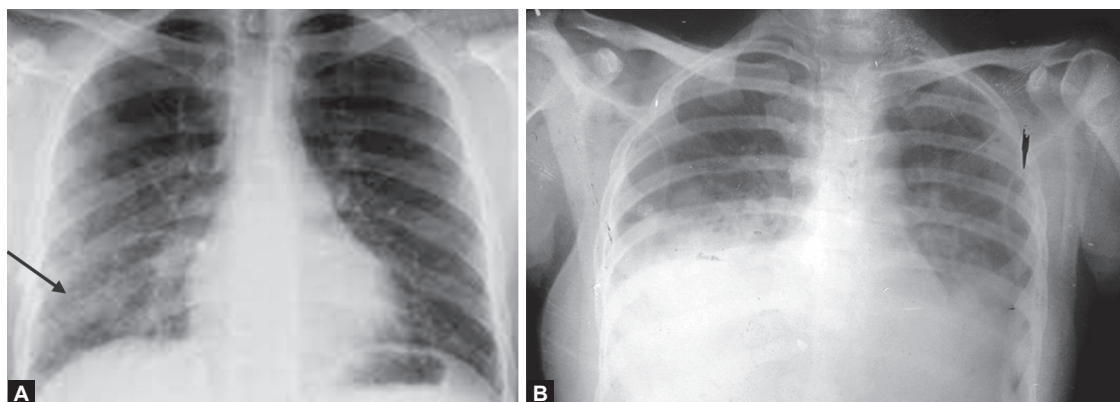
KEROSENE OIL POISONING (FIGS 37.1A AND B) (Kerosene Poisoning)

It is the most common accidental poisoning seen in pediatric practice in our as well as other tropical countries. Kerosene is an aliphatic (open chain), moderately toxic, low viscosity <60 Saybolt universal second (SSU) hydrocarbon posing significant hazard of aspiration and chemical pneumonitis.

There is virtually no GI absorption of kerosene. CNS toxicity results from hypoxia secondary to aspiration pneumonia. This could be enhanced by the volatility of kerosene at body temperature causing toxicity through inhalation and asphyxia by vapors. No CNS depression occurs in the absence of pulmonary complications. Fatal systemic absorption from topical exposure has been reported in very young infants.

Clinical Features

- Earliest symptom is violent coughing, choking and flushing of the face immediately following ingestion. Some aspiration may occur following this.



Figs 37.1A and B: Chest X-ray in kerosene oil poisoning. (A) This X-ray, done at the beginning, shows only right lower lung infiltration and pulmonary edema; **(B)** This Chest X-ray, done a few days later, shows frank lower lobe consolidation with pleural effusion (note blunting of right costophrenic angle).

- Vomiting shortly after its ingestion may bring out ingested kerosene in some cases. One can usually find smell of kerosene from the mouth and vomitus.
- Headache, abdominal pain, vomiting, diarrhea and dryness of throat are often encountered in older children.
- Fever, breathlessness, GI bleeding in a proportion of cases.
- Pneumonia, complicating the situation in about 25% children, is a troublesome complication. Any child with choking cough or vomiting at the time of ingestion should be considered to have aspirated until proved otherwise even if child appears asymptomatic in emergency department.
- Cardiac arrhythmias and renal failure are infrequent.
- Occasionally, CNS complications in the form of seizures and coma may occur.

Diagnosis

Over and above the information from history and circumstantial evidence, a peculiar odor in the breath, vomitus and urine supports the diagnosis. It is advisable to have a chest X-ray to exclude aspiration pneumonia which usually takes a few hours to manifest. In the beginning CXR may show only some infiltration and pulmonary edema. ECG is indicated in case development arrhythmias. In severely affected patients, it is appropriate to do ABG analysis for documenting hypoxemia.

Complications

These include:

- **Respiratory:** Pneumonia, pneumatocele, pleural effusion/empyema, pneumothorax, pneumomediastinum, atelectasis and lung necrosis, etc.
- **CNS:** Seizures, encephalopathy causing coma.
- **CVS:** Arrhythmias and myocarditis.

Treatment

Asymptomatic Cases

Most of the children are asymptomatic and can be discharged safely after 6 hours of observation for aspiration and pneumonia in particular. Several studies have documented that as much as 20 mL/kg of kerosene can be safely ingested without systemic toxicity.

Symptomatic Cases

- Oxygen and respiratory support should be provided to the symptomatic children.
- Decontamination of the skin and removal of contaminated coverings avoids continued dermal absorption.
- Gastric lavage or induced vomiting is best avoided even in situations where large amounts >2 mL/kg have been ingested.
- Prophylactic antibiotics are of value only in case of a superimposed infection. Else, antibiotics as well as steroids are of no value.

Prognosis

Most symptomatic patients show improvement in 24 hours or so with resolution of the symptoms within a week.

ORGANIC PHOSPHATE POISONING

Accidental ingestion of organic phosphates, generally in the form of insecticides and pesticides (say Tik-20), is fairly common in childhood. They cause inhibition of cholinesterase, resulting in accumulation of acetylcholine and stimulation of CNS and parasympathetic system. Absorption of organic phosphates occurs not only from mucosa, but also from the skin.

Clinical Features

- Within a few hours, the poisoning manifests in the form of blurred vision, headache, weakness, diarrhea, pain in the abdomen and chest, and nausea.
- Pulmonary edema and respiratory distress may result from excessive secretions in the lungs.
- Salivation and sweating are profuse.
- Muscle twitching, convulsions, loss of reflexes and coma may occur in advanced cases.
- Sphincter control is lost by many patients.
- A remarkable finding is the constriction of the pupils and, at times, papilledema.

Diagnosis

Diagnosis, though nearly always clinical, may be confirmed by reduced red cell cholinesterase.

Treatment

As soon as the diagnosis is reached, stomach wash should be done with soap and water. Remember never to give morphine.

Complete atropinization is, however, the specific treatment. The initial dose is 0.03–0.04 mg/kg to be given intravenously (IV). Half of this dose needs to be repeated every 15–30 minutes until pupils begin to dilate (mydriasis), mouth becomes dry and tachycardia results.

Along with atropinization, it is necessary to administer pralidoxime IV. The dose is 25–50 mg/kg which should be injected over a 5 minute period slowly. Supportive measures including oxygen, artificial respiration and postural drainage of secretions, may be warranted in serious cases.

DDT POISONING

Poisoning from dichlorodiphenyltrichloroethane (DDT), a white powder with mild smell, is quite frequently encountered in childhood. Despite its having been recently condemned as an **environmental pollutant**, its benefits in health programs outweigh its hazards and it continues to be widely used for spray in the houses against malaria and other diseases.

Clinical Features

- Neurological manifestations are the hallmark of accidental swallowing of DDT.
- Confusion, tremors, incoordination and seizures.
- Paresthesia involving lips, tongue and face may occur.

728 Treatment

It is purely symptomatic. Control of seizures with phenobarbital or diazepam should be immediately achieved. As yet there is no specific antidote for DDT poisoning.

BARBITURATE POISONING

Unlike the experience reported from the western countries, accidental barbiturate poisoning is not a frequent pediatric emergency in our set up.

Clinical Features

- Considerable drowsiness is the most usual presenting feature.
- Vomiting is common.
- Restlessness and flushing are occasionally seen.
- A serious case may present in coma with:
 - Respiratory depression
 - Acute kidney injury
 - Acidosis
 - Shock
 - Pulmonary complications.

Treatment

Majority of the children with barbiturate poisoning respond well to simple gastric lavage. Presence of cyanosis is an indication for oxygen inhalation. IV fluids are indicated in the presence of shock, acidosis or renal failure. Rarely, a resort to peritoneal dialysis becomes necessary. Respiratory stimulants, like bemegride, are no longer recommended in the management. Severe respiratory difficulty may need tracheostomy to maintain an open airway.

PARACETAMOL (ACETAMINOPHEN) TOXICITY

With increasing use of paracetamol as an analgesic/antipyretic agent, the incidence of its toxicity has geared up. Almost always, significant toxicity occurs in children above 6 years of age.

Modus Operandi

Mercuric acid conjugate, a metabolite of paracetamol, is the central factor in causing toxicity.

Clinical Features

Four clinical stages of paracetamol toxicity are recognized (Box 37.4).

Treatment

N-acetyl-L-cysteine (NAC) is the antidote of choice. It is best given within 16 hours after ingestion and in no case beyond 24 hours. In view of the significant higher incidence with IV infusion of hepatotoxicity, it is administered orally as a loading dose of 140 mg/kg followed by 70 mg/kg at 4 hour intervals for 17 additional doses.

Prognosis

Prognosis in treated cases is excellent. Even with serious hepatotoxicity, complete recovery occurs in 99.5% cases.

Box 37.4 Four clinical stages of paracetamol toxicity

- **Stage I:** It lasts from 1/2 to 24 hours after ingestion and is characterized by anorexia, nausea, vomiting, pallor, lassitude and diaphoresis.
- **Stage II:** It lasts from 1–2 days after ingestion and is characterized by resolution of manifestations of stage I and appearance of pain in the upper abdomen, oliguria and liver dysfunction (raised serum bilirubin, FT, SGOT, SGPT).
- **Stage III:** It lasts from 2–4 days after ingestion and is characterized by reappearance of anorexia, nausea, vomiting and pallor, plus peak liver dysfunction.
- **Stage IV:** It lasts from 4 days to 2 weeks after ingestion and is characterized by resolution of liver dysfunction. In a suspected case of paracetamol toxicity, plasma level should be measured at 4 or more hours following ingestion. Once the diagnosis is established, serum bilirubin, AST (SGOT) and ALT (SGPT) evaluation and FT evaluation must be followed daily.

Abbreviations: SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

IBUPROFEN TOXICITY

With increasing use of the anti-inflammatory agent, ibuprofen, it is likely to be involved in overdoses (both accidental and intentional), leading to toxicity and poisoning in children.

- Normal blood levels at 2 hours of ingestion are 70–100 µg/ml.
- If the level is 80–200 at 3 hours, mild GI manifestations occur.
- At 2 hour level of 360 µg/mL, serious toxicity occurs.
- A dose of over 1000 mg/kg is likely to be toxic.

Clinical Features

- Nausea, epigastric pain, upper GI bleed, lethargy, apnea, drowsiness and coma.
- Renal failure, hypotension, nystagmus, diplopia, tinnitus, deafness, headache, acidosis and remarkable elevation in serum potassium and creatinine and blood urea nitrogen are encountered in some cases.
- Occasionally, ibuprofen may cause anaphylactoid reactions in the form of circulatory collapse, pruritus and angioedema.

Treatment

The patient must be provided good supportive care for respiration, cardiovascular system and coma. Emesis and/or gastric lavage together with charcoal hypoperfusion, dopamine in case of hypotension and hemodialysis are beneficial. Since 90% ibuprofen is protein-bound, alkaline diuresis is of no value.

ASPIRIN POISONING

(Salicylism)

Incidence of accidental aspirin poisoning in the developing World as well as is on the increase. In a child with such a poisoning, the blood salicylate level is usually above 40 mg%.

Clinical Features

- The most remarkable feature of aspirin poisoning is what has come to be designated as *air-hunger*.
- Respiration is deep and rapid without a pause. This picture contrasts with the short and grunting breathing seen in case of pneumonia.
- Nausea, vomiting, tinnitus and fever may also be present.
- Eventually, the child becomes cyanotic. A full-fledged peripheral circulatory failure may develop. Twitching, convulsions, rigidity and coma are often the terminal events.

Treatment

It includes measures such as *induced vomiting* and/or gastric lavage, oxygen inhalation, IV drip and peritoneal dialysis. Some workers have reported excellent results following exchange transfusion.

PHENOTHIAZINE TOXICITY

In recent years, an increasing number of children are being reported to hospitals with neurologic manifestations following administration of triflupromazine, prochlorperazine, chlorpromazine or some other phenothiazine. These drugs may produce toxicity in therapeutic as well as toxic doses.*

Concomitant administration of chloroquine, amodiaquine, metoclopramide, haloperidol, phenytoin, diazoxide, lithium, reserpine, chlorprothixene as also presence of dehydration boosts the risk of phenothiazine toxicity, both in frequency and severity.

Clinical Features

- Clinical picture is dominated by acute onset of signs and symptoms pertaining to extrapyramidal system.
- The characteristic features are choreiform movements, torticollis, muscle rigidity, opisthotonos, marked deviation of eyes and oculogyric crisis.
- Trismus, swallowing difficulties, drooling, tremors and ataxia may also occur. Convulsions and coma are rare.

Treatment

Diphenhydramine hydrochloride, 2 mg/kg (maximum 50 mg total), given slowly by IV route over a period of 3–5 minutes, is a highly effective antidote. Dramatic response occurs after the injection in a large majority of the cases. This agent is effective orally either, but the response is rather slow. Promethazine 0.5 mg/kg, given intramuscularly (IM) is another useful agent. Administration of 0.5 mg of physostigmine IV, over a period of 5 minutes also gives gratifying results. It acts through its anticholinesterase property. More recently, parenteral diazepam has yielded excellent results.

CHLOROQUINE-INDUCED PSYCHOSIS

Infrequently, chloroquine, irrespective of the dose, may induce transient psychotic manifestations.

Clinical features:

- Change in sensorium, confusion and disorientation
 - Outbursts of violence and aggressive behavior
 - Hallucinations, including the visual ones in the form of the so-called *Alice-in-Wonderland syndrome*.
- **Treatment:** Following withdrawal of chloroquine, complete reversal of the manifestations results within hours to days. There is no residual symptoms. Administration of diazepam speeds up recovery.

CYPROHEPTADINE POISONING

Cyproheptadine has therapeutic dose of 0.25 mg/kg/day, toxic dose 4–8 times the therapeutic dose and fatal dose 25–250 mg/kg.

Large doses may cause two opposing syndromes.

1. Depression may occur in the form of drowsiness, disorientation, staggering, hallucination, stupor and coma.
2. Stimulatory manifestations may include excitement, fever, hyperreflexia, nystagmus and seizures.

Treatment consists of administering chlorpromazine, neostigmine and, in case of seizures, diazepam along with stomach wash and IV fluids. Prognosis, following timely and appropriate treatment, is gratifying.

IRON (IRON SALTS) POISONING

Accidental ingestion by the child of a large number of medicinal iron (usually ferrous sulfate) tablets, often available in the house for the use of the mother, is a common problem. Toxicity follows at serum level >500 µg/dL. Lethal dose of elemental iron is about 250 mg/kg or more.

Clinical Features

- The 250–300 µg to the gastric mucosa may cause severe GI bleeding resulting in hematemesis and bloody diarrhea.
- Shock, CNS depression and hepatic or renal failure may occur within few hours or after a day or two.
- Incidence of pyloric stenosis as a late sequel is high.

Diagnosis

Though it is by and large clinical, abdominal X-ray (Fig. 37.2) may show radioopaque material which indirectly points to a serum iron level of >250–300 µg/dL.

Other indices favoring toxicity include:

- Blood sugar is more than 150 mg/dL
- Total leukocyte count is more than 15,000/mm³.

Treatment

Immediately on diagnosis, vomiting should be induced and stomach wash done with sodium bicarbonate (NaHCO₃).

For shock, an IV drip is started. A careful monitoring to maintain fluid, electrolyte and acid-base balance is essential. Desferrioxamine, 90 mg/kg/day in 4–6 divided doses IV or IM, is the antidote. The total calculated dose may

* Phenothiazines can also produce dangerous hypersensitivity reactions like agranulocytosis, hepatitis and dermatitis.



Fig. 37.2: Abdominal X-ray in iron poisoning. Note the opacities reflecting iron deposits in the gut.

well be given by IV or subcutaneous drip in 12–24 hours. The drip method has, in fact, proved to be most effective. If desferrioxamine is not available (which is usually the case in our country), give the patient 12.5 mg/kg of calcium ethylenediaminetetraacetic acid (EDTA) IM. Occasionally, in case of renal failure a dialysis or exchange transfusion may become necessary.

MORPHINE AND OTHER OPIATES POISONING

It can occur in three ways:

1. Accidental ingestion of large dose
2. Excessive therapeutic administration
3. Breastfeeding by a mother taking the agent.

Clinical Features

The salient clinical features are:

- Respiratory depression
- Change in sensorium to the extent of coma with pin-point pupils
- Vomiting.

Treatment

Specific antidote is nalorphine. It should be given in a dose of 0.1 mg/kg stat. Other measures include stomach wash with potassium permanganate and oxygen inhalation.

DHATURA POISONING

(Atropine Poisoning, Belladonna Poisoning)

Datura poisoning usually occurs when children accidentally swallow datura seeds.

Clinical Features

- Flushing of the face, dry skin and mucus membrane, dilated pupils, blurring of vision, fever and tachycardia.

- Initially the patient is restless, but soon goes into depression, shock and coma.
- Respiratory collapse may occur.
- Retention of urine is common.
- Many patients develop abdominal distention.
- Children with atropinism have been described as—red as beet, dry as bone, and mad as a hatter.

Treatment

Specific antidote is physostigmine, 0.5–2.0 mg (0.1 mg/kg/dose) IV slowly stat. It can be repeated every half an hour if needed. Other measures include induction of vomiting and/or stomach wash, control of fever by hydrotherapy and/or antipyretics, sedation to calm down the patient and catheterization in case of prolonged retention of urine.

LEAD POISONING

(Plumbism)

It usually occurs in children suffering from pica involving ingestion of lead paint flakes, artist's paints, etc. from inhalation of fumes from batteries and from practice of employing kajal/surma containing black oxide of lead in eyes.

Clinical Features

- Transient abdominal pain, resistant anemia, loss of weight, irritability, vomiting, constipation, headache, personality changes and ataxia are its common symptoms.
- Poor physical development, seizures, and raised intracranial pressure leading to coma (lead encephalopathy) are rather late manifestations.
- A lead line in the gums is characteristic.

Diagnosis

Urine lead level of more than 80 µg/dL/24 hours is diagnostic of lead poisoning. Blood lead level in symptomatic cases usually exceeds 80 µg/dL. Urinary coproporphyrins or red cell aminolevulinic acid dehydrase levels are also good screening tests. Peripheral blood film shows normocytic-hypochromic anemia with reticulocytosis and basophilic stippling of red blood cells (RBC) (Fig. 37.3).

X-rays may reveal opaque flakes in the GIT. Screening of the bony skeleton may show a lead line at the metaphyseal areas. CSF pressure, proteins and cell count are moderately raised.

Treatment

In case of sudden massive ingestion of lead, it is advisable to induce vomiting followed by administration of a saline cathartic.

Specific treatment is a combination of dimercaprol British antilewisite (BAL), 4 mg/kg/dose every 4 hours IM, and calcium EDTA, 12.5 IV mg/kg/dose every 4 hours IM or IV. After 2 day therapy with these drugs, there is need to stop them and give penicillamine, 25 mg/kg/day orally for 5 days.

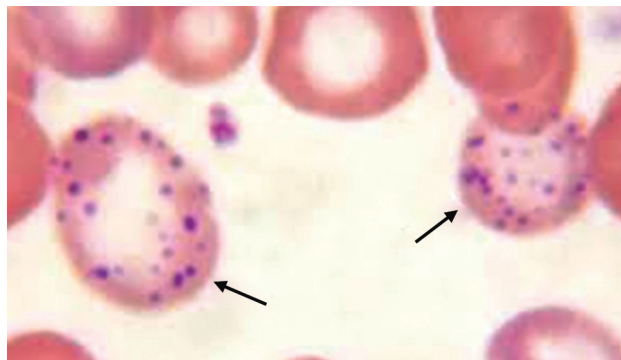


Fig. 37.3: Peripheral blood film in lead poisoning. Basophilic stippling along with microcytic hypochromic anemia is noticeably remarkable. This type of picture is seen in hemolytic anemias (thalassemia intermedia and major).

Remember that chelating therapy is not indicated when lead levels are below 60 µg/dL unless indicated by an additional evidence of lead toxicity. In case of encephalopathy, anticonvulsants, mannitol and/or steroids are indicated. Do not use BAL in presence of hepatic insufficiency. Do not give iron while therapy with BAL is in progress. Remember too that a high calcium, high phosphorus diet and massive doses of vitamin D are of value in removing lead from blood and depositing it in the bones.

MERCURY POISONING

Mercury poisoning may be acute or chronic and reversible or irreversible, depending on the compound and extent of exposure. It may occur from excessive inhalation of the mercurous vapors, oral intake or repeated contacts with mercury-containing products like paints, wall-papers, diaper rinses, etc.

Acute Mercury Poisoning

Clinical Features

It is characterized by predominantly GI and renal manifestations. In case of an exposure to high concentration of mercury vapor, manifestations include pulmonary irritation or pneumonitis, nausea, vomiting, diarrhea, abdominal pain and headache.

In oral exposure to mercury, manifestations include stomatitis, gingivitis, esophagitis, gastroenteritis with consider-

able salivation, abdominal pain and bloody diarrhea. In case of renal damage, albuminuria, and uremia may develop. CNS manifestations like ataxia, slurring of speech, visual and hearing impairment, numbness of hands and feet and delirium may occur.

Treatment

It consists of removal of mercury in stomach by gastric lavage (first with milk and then with sodium bicarbonate), correction of fluid and electrolyte imbalance, peritoneal or hemodialysis for acute renal failure, and symptomatic measures for restlessness and tachycardia. Specific antidote is dimercaprol or BAL. Alternatively, penicillamine is recommended in case of adverse reactions to BAL.

Chronic Mercury Poisoning

It is characterized by predominantly CNS and skin manifestations. It is rare in children. **Acrodynia** and **Minamata disease** are two well-recognized forms of pediatric chronic mercury poisoning.

Acrodynia

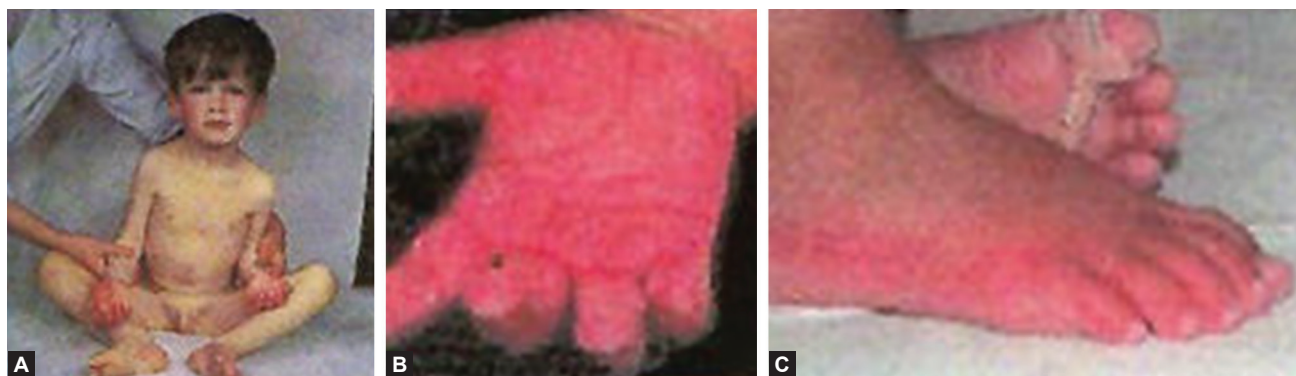
(Pink Disease)

It is an unusual reaction to repeated ingestion of or contact with mercury. The clinical appearance and course of the disease are very characteristic. Extreme hypotonia, photophobia, pinkish color of extremities with hands and feet which are often red and painful (Figs 37.4A, B and C) and marked dejection and melancholia are the outstanding features. Urinalysis shows presence of mercury.

The disease runs a prolonged course, some patients dying especially as a result of superadded infections. Treatment is difficult. Administration of BAL, steroids and sedation, and symptomatic measures are of value.

Minamata Disease

It is caused by ingestion of contaminated fish and shell fish. Between 1953 and 1966, it occurred in epidemic proportion in certain towns facing Minamata Bay in Japan. Manifestations include disturbances in hand coordination, gait and speech, chewing and swallowing difficulties, visual



Figs 37.4A, B and C: Mercury poisoning. Note the photophobia, lesions over extremities and hand and feet which are reddish and painful.

732 blurring, tremors, rigidity, seizures and cloudiness of consciousness. Occasionally, impaired hearing and constriction of visual field may occur.

In congenital form, resulting from fetal poisoning from the mother who has eaten contaminated fish, more severe and widespread brain damage may lead to physical, motor and mental retardation, abnormal movements, or lack of smoothness of movements.

Besides symptomatic treatment in the form of anticonvulsants and good nourishing diet, BAL is effective in removing systemic mercury from the body. The CNS damage being irreversible, survivors need rehabilitation, re-education and long-term care.

LATHYRISM

Lathyrism, a crippling neurologic disease, results from excessive consumption of a wild pulse (legume), *Lathyrus sativus*, which is popularly known by such names as **khesri daal, teora daal or lakh daal**. The pulse looks like **Bengal gram or red gram daal** and is consumed by the poor for economic reasons, or is used for adulteration of relatively expensive **Bengal gram daal**.

The disease is reported mainly from India (especially central and northwestern parts where it is a public health problem) and Bangladesh though Greece, Germany, Russia, France, Spain, Syria, Italy, Algeria, Abyssinia, Iran and Afghanistan are also on record for its existence. The basic causative factor for neurologic manifestations in the pulse is a neurotoxin, betaoxalyl aminoalanine (BOAA), though several additional toxic factors are also contained in the seed. For development of lathyrism, it is necessary that the pulse is consumed in a large quantity (30–40% of total dietary intake) over a prolonged period (2–6 months).

Lathyrism has a greater tendency to inflict the children and youth, especially the males. Manifestations include a progressive spastic paralysis of lower limbs.

A ban on cultivation of the pulse is the only sure method of prevention. Alternative recommendations are an intensive educational campaign against consumption of the pulse and, if consumption becomes unavoidable, removal of the water-soluble toxin by simple measures such as parboiling or soaking the pulse in hot water and draining away the soaked water.

Multiple Choice Questions

- In management of a child unconscious from poisoning the first thing to do is to:
 - Establish airway
 - Take detailed history
 - Blood for chemical analysis
 - Gastric washout
- The major toxicity of acetaminophen overdose includes:
 - CNS
 - Heart
 - Liver
 - Metabolism
- A comatose child has garlic like odour to the breath. The most probable diagnosis is:
 - Flavism
 - Atropine poisoning
 - Lead poisoning
 - Arsenic poisoning
- A 3-year-old child has features of gripping abdominal pain, severe vomiting, bloody diarrhea, fever and opacities on X-ray abdomen. The most likely diagnosis is:
 - Iron poisoning
 - Lead poisoning
 - Phosphorous poisoning
 - Magnesium poisoning
- Incorrect observation about kerosene oil poisoning is:
 - Induced vomiting is strongly recommended when the child has ingested 2 mL/kg or more of kerosene
 - Chest X-ray is likely to show evidence of pneumonia after a few hours of ingestion rather than soon after
 - Infrequently, cardiovascular complications in the form of arrhythmias and myocarditis may occur
 - Virtually no gastrointestinal absorption of kerosene occurs
- All of the following observations about paracetamol poisoning are true, except:
 - Mercuric acid conjugate, a metabolite of paracetamol, is the central factor in causing toxicity
 - Stage 3 poisoning is characterized by pain in the upper abdomen, oliguria and liver dysfunction (raised serum bilirubin, FT, SGOT, SGPT)
 - Antidote of choice is N-acetyl-L-cysteine (NAC)
 - In adequately treated cases, prognosis is excellent with complete recovery

contd...

7. Manifestations such as pica, transient abdominal pain, resistant anemia, loss of weight, irritability, vomiting, constipation, headache, personality changes and ataxia together with peripheral blood picture showing microcytic anemia with basophilic stippling suggests diagnosis of:
- A. Iron poisoning
B. Lead poisoning
C. Arsenic poisoning
D. Ibuprofen poisoning
8. Type of respiration in morphine poisoning is:
- A. Deep Rapid
B. Rapid Shallow
C. Slow Depressed
D. Diaphragmatic fast

Answers

1. A 2. C 3. D 4. A 5. A 6. B
7. B 8. C

Clinical Problem-solving**Review 1**

A 9-year-old child presents with severe hypotonia, photophobia, pinkish color of extremities with hands and feet which are red and painful. Over and above this picture, the child shows signs of marked dejection and melancholia.

1. What is the diagnosis?
2. How to confirm its diagnosis?
3. What is its treatment?
4. What is the prognosis?

Review 2

A 5-year-old child presented with profuse salivation and sweating, breathlessness, blurred vision, headache, weakness, diarrhea, pain in the abdomen and chest, and nausea of 3–4 hours duration. Parents suspect his having taken by default an insecticide. During examination, he is also found to have muscle twitching and loss of sphincter control. Pupils are constricted.

1. Your diagnosis?
2. What is the mechanism of action of the concerned poison/toxin?
3. How to confirm clinical diagnosis?
4. What is the antidote-based therapy?

Answers**Review 1**

1. Acrodynia which is a chronic mercury poisoning.
2. Urinalysis shows presence of mercury.
3. BAL is the antidote for mercury poisoning. Along with this antidote, symptomatic therapy, steroids and sedation may be needed.
4. Acrodynia runs a protracted course. Superadded infections prove fatal in a proportion of cases.

Review 2

1. Organophosphate poisoning.
2. An organic phosphate compound causes inhibition of cholinesterase, resulting in accumulation of acetylcholine and stimulation of CNS and parasympathetic system. Its absorption occurs not only from mucosa, but also from the skin.
3. By demonstration of reduced red cell cholinesterase.
4. Atropinization along with intravenous pralidoxime intravenously.

FURTHER READING**JOURNAL ARTICLES/BOOK CHAPTERS**

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BOOK/MONOGRAPH

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SNAKE BITE

Snake bite is a common emergency, particularly among children living in slums and villages. India is known for the highest snakebite mortality in the world. World Health Organization (WHO) estimates place the number of snakebites at 83,000 per annum with 11,000 deaths.

There are about 236 species of snakes in India. Only 13 species are known to be poisonous. Three types of poisonous snakes encountered in India are:

1. **Neurotoxic:** Cobra which causes paralysis of muscles of eyes (ptosis in particular), palate, jaws, tongue, larynx, neck, deglutition and chest, eventually leading to respiratory failure. Cardiotoxicity (hypotension, tachycardia, electrocardiograph {ECG} alterations) and hemolysis may also occur. Onset of manifestations is rapid.
2. **Hemorrhagic hemotoxic:** Viper which causes tissue destruction, hemorrhage and has relatively slow onset of symptoms.
3. **Neurohemotoxic:** Krait which contains both neuro and hemotoxins. It is the most common and dangerous poisonous snake in India.

Clinical Features

Clinical symptomatology of snake bite is termed as **ophitoxemia**. Any snake (poisonous or non-poisonous) may cause shock. Apart from the bite, the sheer appearance of a snake may be frightening.

Local Manifestations

Locally there may be just fang marks and even bruises and lacerations, oozing of serosanguinous fluid in case of viper bites, pain, swelling, redness and numbness at the site of bite.

Constitutional Manifestations

- Constitutional symptoms appear after about 15–30 minutes of bite and include headache, dizziness, nausea, vomiting and abdominal discomfort/pain.
- Central nervous system (CNS) stimulation, convulsions followed by depression, respiratory difficulty and various paralysis.
- Hemorrhage from different sites and circulatory collapse may occur. Hemorrhagic sting is most dreaded manifestation which includes bleeding from fang punctures, venipuncture sites, ecchymosis, epistaxis bleeding gums, subconjunctival and intracranial bleeding.
- Intracranial bleeding is the usual cause of death within 24–48 hours.

Box 38.1 Grading of envenomation in snake bite

- **Grade 0:** Nil
- **Grade 1:** Minimal, with local swelling and pain that does not progress
- **Grade 2:** Moderate, with swelling, pain or ecchymosis progressing beyond the location of bite and also mild systemic and laboratory abnormalities
- **Grade 3:** Severe, with remarkable local response, severe systemic findings and significant alteration in laboratory tests.

Laboratory Investigations

- Laboratory investigations are useful only for monitoring the patient.
- Baseline investigations should include hemoglobin, complete blood count, platelet count, clotting time, prothrombin time, partial thromboplastin time, blood urea nitrogen, creatinine, creatine phosphokinase (CPK) and ECG.
- Anemia, thrombocytopenia, leucocytosis, hypofibrinogenemia, proteinuria, azotemia, ST-depression/elevation, T inversion, QT prolongation and arrhythmias are common abnormalities.
- Immunodiagnosis by enzyme linked immunosorbent assay (ELISA) is useful (if available) to detect specific snake venom in wound aspirate, serum or other body fluids.

Grading of Envenomation

Clinically and on investigations, envenomation may be graded as per Box 38.1.

Treatment

Immediate Measures

These should be directed at allaying fear, treating shock and respiratory failure with all available means. Patient should be kept recumbent, quiet and reassured. Only 25% of the snakes are considered poisonous. Wound should be cleaned with saline/water.

During transportation to the hospital, to prevent absorption of toxin, a tourniquet is often applied. This practice is best discouraged. Else, it must be ensured that tourniquet is proximal to the bite about 5 cm above the upper limit of swelling, allowing one finger beneath. It should be left in situ as long as antivenom serum (AVS) is not given. Furthermore, the following "do not's" are important in the first-aid handling of the child:

- Do not wash the bite site with soap or any other solution to remove the venom.

Box 38.2 Components of the mnemonic—RIGHT in management of snake bite

R: Reassuring the patient.

I: Immobilization of the bitten part and placed in a dependent, but functional position below the level of the heart.

G and H: Get to the Hospital immediately.

T: Tell the doctor of any symptoms during transit.

- Do not make cuts or incisions on or near the bitten site.
- Do not use electrical shock.
- Do not freeze or apply extreme cold to the bite site.
- Do not apply any kind of potentially harmful herbal or folk remedy.
- Do not attempt to suck out venom with application of mouth to the bite.
- Do not give alcohol to the victim.
- Do not take the patient to a quack.
- Do not attempt to capture, handle or kill the offending snake.

The bitten part should be immobilized and placed in a dependent position. The mnemonic RIGHT is worth bearing in mind the measures aimed at reducing spread of venom and expediting transportation to the nearest facility where AVS can be given if the need arises (Box 38.2).

Specific Measures

Definitive indications for AVS are listed in Box 38.3. Presence of fang marks, local pain, edema, swelling, numbness and weakness indicate the envenomation and AVS must be administered without loss of time after a test for hypersensitivity.

Children require much larger dose since there is higher concentration of venom in terms of body weight. The dose varies from 50–200 mL or even more. It is given as intravenous (IV) infusion by reconstituting with distilled water or normal saline and diluted with 3 volumes of glucose saline beginning at the rate of 1 mL/minute and increased slowly as tolerated usually 20 mL/kg/hour. Ideally AVS should be given as early as possible, but it may be efficacious even up to 1 week after the bite.

Injection of a part of antiserum locally is unnecessary; so are direct application of ice, local incision and oral suction. Concurrent administration of steroids and antihistamines reduce the risk of anaphylaxis due to antivenin. **AVS hypersensitivity** may be tested by the following methods:

- History of allergy to AVS or some other horse serum in the past.
- Skin test by intradermal injection of 0.1 mL of 1:100 saline dilution of AVS. Hypersensitivity is indicated by appearance of a wheal (>10 mm) in 10–30 minutes.

Box 38.3 Definitive indications for AVS in snake bite

- **Systemic envenomation:** Bleeding, DIC, shock, AKI, neurotoxicity
- **Swelling over snake bite site** that shows progressively spreading or bleeding.

Abbreviations: AVS, antivenom serum; DIC, disseminated intravascular coagulation; AKI, acute kidney injury.

- Conjunctival test by instilling one drop of 1:10 dilution in saline in lower conjunctival sac. Hypersensitivity is indicated by development of conjunctivitis and tears in 10–30 minutes.

Desensitization

Desensitization is carried out by intradermal injection of 0.1 mL of 1:100 saline dilution of AVS. Every 15 minutes the injection is repeated with a gradually increased dose of AVS until dose of 1 mL subcutaneously (SC) is given. This is followed by administration of 0.1 mL of undiluted AVS which again is built up to 1 mL gradually.

If all goes well, 10 mL AVS diluted in 500 mL of normal saline is infused IV by slow drip. Subsequently total calculated dose is administered carefully. Preparedness to manage anaphylaxis should always be there in the form of availability of epinephrine (dose 0.01 mg/kg IM).

Role of neostigmine: Neostigmine, an anticholinesterase, is particularly effective in postsynaptic neurotoxins such as those of cobra. Neostigmine test needs to be performed by administering 0.5–2 mg of the agent intravenously. If neurological improvement occurs, neostigmine should be continued every half hourly over next 8 hours.

Supportive Measures

- Prophylaxis against tetanus and gas gangrene should be given.
- Antibiotics are needed in the presence of superimposed infection.
- Whole fresh blood or fresh frozen plasma transfusion for life-threatening bleeding.
- Restriction of fluids and electrolytes in acute kidney injury (AKI).
- Surgical debridement in case of gangrene may be needed.
- **Follow-up:** If discharged within 24 hours, the parents should be advised to bring back the child in case of any further bleeding, pain or swelling at the bite site, dyspnea, altered sensorium, etc. The parents should also be explained about serum sickness that may manifest after 5–10 days.

Prevention

Overall mortality due to snake bite is about 10%. In snake-infested areas, use of boots, socks, trousers and torch may prevent snake bites.

Complications

Box 38.4 lists the common complications, including compartment syndrome.

SCORPION STING

Two species of scorpion namely *Mesobuthus tamulus* and *Palamnaeus swammerdami* are poisonous in India.

Scorpion venoms are species-specific complex mixtures of short neurotoxic proteins containing free amino acids, serotonin, hyaluronidase and various enzymes. Voltage dependent ion channels are altered by the venom

Box 38.4 Complications of snakebite

- Compartment syndrome characterized by **six Ps**, namely:
 - **P**ain out of proportion to injury
 - **P**ressure symptoms in the form of swollen part
 - **P**aresthesia
 - **P**ain with passive stretch
 - **P**aresis/paralysis
 - **P**ulse being absent
- Tissue necrosis (Fig. 38.1)
- Bleeding diathesis.



Fig. 38.1: Snake bite. Note the hematoma over the site of bite and a patch progressing to necrosis.

resulting in alpha receptor stimulation. It is responsible for autonomic storm. Local inflammation is unusual in Indian red scorpion envenomation.

Clinical Features

Species differences, venom dose/weight relationship determine the toxicity and clinical picture. Symptoms progress to a maximal severity in about 5 hours and subside within 24–48 hours. Based on symptomatology, the stings can be divided into benign, potentially dangerous and invariably fatal.

Benign Stings

Extreme local pain within seconds to minutes and little or no reaction at sting site. Serotonin found in the scorpion venom is responsible for pain.

In **tap test**—severe pain by tapping over the sting site is often seen in Indian patients; however some children complain of pain at the site during recovery or paresthesia around the sting. Patients with severe local pain often do not have further progression of symptoms.

Potentially Dangerous Sting

It is characterized by features of **autonomic storm**. Cholinergic stimulation (hypovolemia) merges imperceptively into adrenergic stimulation (ionotropic phase) and if treated properly the recovery follows in next 48–72 hours, Box 38.5 shows features of autonomic storm.

Box 38.5 Clinical features of autonomic storm in potentially dangerous scorpion stings

Mild pain, paresthesia vomiting, sweating salivation	→ Hypovolemia
Priapism, cool limbs tachycardia hypertension	→ Ionotropic phase
Myocardial dysfunction, arrhythmia, shock	→ Pulmonary edema

Fatal Sting

These patients have predominant CNS manifestations within 1–2 hours of sting. It occurs infrequently, but invariably fatal. Encephalopathy, convulsions, aphasia hemiplegia, cerebral hemorrhage, disseminated intravascular coagulation (DIC) and central respiratory failure have been reported. Aggressive supportive measures may reduce the mortality.

Treatment

The treatment should be directed to relieving pain, anxiety, suppress autonomic storm, correction of hypovolemia and pulmonary edema. Antivenom against the toxins of Indian scorpions is now available (though not freely) for clinical use. It may not alter the course if given 30 minutes or more after the sting, since scorpion venom reaches the target tissues too rapidly to be neutralized.

Prazosin, a competitive postsynaptic alpha adrenoceptor antagonist, is the first line management. The time lapse between the sting and prazosin administration for control of autonomic storm symptomatology determines the outcome. It reverses the metabolic and hormonal effects of alpha receptor stimulation and thus it is a cellular and pharmacologic antidote to the reactions of scorpion venom in addition to being cardioprotective. Dose recommended is 30 µg/kg/dose. It may be repeated after 3 hours and then every 6 hours till improvement. Monitoring of vitals is essential. Prazosin should be given only if the clinical features suggest autonomic storm and not prophylactically. If only pain is present, hypovolemia should be corrected immediately before giving prazosin.

Pain can be relieved with nonsteroidal anti-inflammatory drugs (NSAIDs), local ice packs, 2% xylocain or dehydroemetine locally. Diazepam is useful to quieten the restless child; allays anxiety and in turn prevents myocardial stress. Encourage oral fluid intake and give IV fluids judiciously to avoid hypovolemia as well as pulmonary edema. Central venous pressure (CVP) line is essential.

Pulmonary edema should be treated by relieving after-load without compromising preload by diuretics, dobutamine (5–15 mg/kg/minute) and vasodilators, sodium nitroprusside (0.3–5 mg/kg/minute) or nitroglycerine (5 mg/minute) infusate.

It is worthwhile to mention that lytic cocktail, morphine, steroids, atropine nifedipine and angiotensin converting

enzyme (ACE) inhibitors are not helpful. In fact, some of them may even worsen the condition. The mortality has decreased dramatically from 30% to below 3% in good centers after introduction of prazosin as the first line treatment.

Mortality

Mortality varies from 4 to 10% in children with systemic envenomation, including those treated in pediatric intensive care unit (PICU).

Multiple Choice Questions

- Spot the wrong observation about snake bite:
 - Krait which contains both neuro and hemotoxins is the most common and dangerously poisonous snake in India
 - Immunodiagnosis by ELISA is useful in detecting specific snake venom in wound aspirate, serum or other body fluids
 - Only 20% snakes are poisonous
 - All of the above
- Usual cause of death within 24–48 hours of snakebite is:
 - Intracranial bleeding
 - Anaphylaxis following AVS
 - Acute kidney injury
 - Compartment of syndrome
- All of the following are components of compartment syndrome, except:
 - Pain out of proportion to injury, pain with passive stretch
 - Pressure symptoms in the form of swollen part
 - Paresthesia, paresis, paralysis
 - Pulsus paradoxus
- Each of the following observations about scorpion sting is correct, except:
 - Autonomic storm forms the core of most serious cases
 - Mortality has decreased dramatically from 30% to less than 3% in good centers after introduction of prazosin as the first line treatment
 - Fatal sting is quite frequent
 - Antivenom may fail to alter the course if given 30 minutes or more after the sting, since scorpion's venom reaches the target tissues too rapidly to be neutralized
- True statements about prazosin include each of the following, except:
 - It is a cellular and pharmacological antidote to the actions of scorpion's venom in addition to being cardioprotective
 - Recommended dose is 30 µg/kg/dose
 - It may be given prophylactically for autonomic symptoms
 - It is important to correct hypovolemia before administering it

Answers

1. D 2. A 3. D 4. C 5. C

Clinical Problem-solving

Review 1

A teenager, aged 17 years, presents with bleeding from multiple sites a few hours after he was bitten by a snake (viper as evidenced by the killed snake they brought in a box). Examinations shows feeble pulses with BP 100/65 mmHg.

- What is the likely cause of bleeding from multiple sites and peripheral circulatory failure?
- Will you give AVS to this child?
- What about blood transfusion?

Review 1

A 6-year-old boy presented with profuse sweating, agitation, tachypnea, tachycardia and priapism following an alleged scorpion sting some 4–5 hours back. A painful swelling with ecchymosis over right foot was evident. BP 115/75 mmHg.

- What is the cause of profuse sweating, agitation, tachypnea, tachycardia and priapism together with hypertension?
- Will it be advisable to immediately administer scorpion antivenom in order to control autonomic symptoms?
- Then, what should be done with this patient?

contd...

Answers**Review 1**

1. Viper is known for hematological manifestations, including defibrination syndrome and DIC. Bleeding may be from prolongation of clotting time or consumption of clotting factor and fibrinogen and even fibrinolysis. In the present cases, since it is from several sites, chances of DIC are high.
Excessive blood loss has seemingly led to peripheral circulatory failure (shock).
2. Yes, we must administer AVS to this profusely bleeding child though the best result with AVS is known to be best when given early enough.
3. Whole blood should logically be avoided since it may worsen the coagulopathy if active venom is still present.

Review 2

1. Apparently, these manifestations are related to autonomic storm which is a known feature of envenomation from scorpion sting.
2. No. Scorpion antivenom is not expected to counter the venom-induced autonomic manifestations. Secondly, its benefit in neutralizing the venom is only when administered within 30 minutes.
3. Over and above local and symptomatic treatment, the well-established pharmacological antidote for the action of scorpion venom, prazosin, should be the first choice. Dose: 30 µg/kg/dose which may be repeated after 3 hours and then 6 hourly until autonomic manifestations are under control.

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The endocrinal system has been aptly compared to an **orchestra**. The hypothalamus acts as the **master** or the **director** whereas the pituitary gland is the **conductor** in this endocrine orchestra. The conductor is subservient to not just the hypothalamus. It is also controlled by the feedback from the glands that it stimulates.

At no other span of life the endocrines and their metabolic and biochemical effects are more important than in infancy and childhood. This is more so since stimulation of physical as also sexual growth is a unique feature of this age.

HYPOTHALAMUS AND ITS DISORDERS

Hypothalamus occupies a unique anatomical as well as functional position. At least five hypothalamic-release factors, namely adrenocorticotrophic hormone (ACTH), growth hormone (GH), thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH) and luteinizing hormone (LH), have been recognized. These factors regulate the activity of anterior and intermediate pituitary glands. Secondly, it produces two neurohormonal substances, namely vasopressin (antidiuretic in action) and oxytocin (stimulates milk secretion and uterine contractions).

DIABETES INSIPIDUS

It is the most common disease that results from the involvement of the neurosecretory system. It is characterized by an inability to concentrate urine, polyuria and polydipsia.

Central Diabetes Insipidus

It is also termed **vasopressin sensitive diabetes insipidus**. It is a chronic disease that results from a defect of the neurohypophyseal system. It is characterized by an inability to concentrate urine, polyuria of 5–20 liters/day and corresponding polydipsia. **Polyuria** may disturb sleep. **Polydipsia** may be as severe as to lead the patients to resort to drinking their own urine at times. Restriction of free fluid intake may lead to severe dehydration, dyselektrolytemia and weight loss.

Etiology

The fundamental defect is deficiency of antidiuretic hormone, **arginine vasopressin**. Hence, the new nomenclature is **vasopressin sensitive diabetes insipidus**.

The causes of neurohypophyseal damage include—craniopharyngioma, optic gliomas and other tumors,

histiocytic infiltration, reticuloendotheliosis, leukemia, encephalitis, tuberculosis, sarcoidosis, actinomycosis, operative procedures or trauma about the base of skull. The genetic forms of the disease (autosomal dominant and X-linked recessive) are also known causes.

Investigations

It shows 24 hour urine output as high as 4–10 (or even more) liters, the specific gravity varying between 1001 and 1005 and the osmolality 50 and 200 Osm/kg water. The 3-hour water deprivation may cause rise in plasma osmolality through the urine osmolality. Radioimmunoassay (RIA), showing vasopressin plasma level below 0.5 pg/mL, is a highly sensitive and more dependable test.

Differential Diagnosis

Differential diagnosis is from **nephrogenic diabetes insipidus** (also called **vasopressin insensitive diabetes insipidus**) compulsive water drinking (psychogenic polydipsia), hypercalcemia, potassium deficiency and chronic renal disorders.

Treatment

Whereas the real treatment should be directed at the underlying cause, symptomatic relief may be obtained with pitressin tannate (oily intramuscular {IM} injection), pitressin snuff or nasal drops, synthetic lysine-8-vasopressin nasal spray, or a vasopressin analogue, desmopressin acetate, intranasally. Chlorpropamide, which is known to potentiate the action of suboptimal amounts of vasopressin, may give satisfactory result in some patients.

Nephrogenic Diabetes Insipidus

It is also called **vasopressin insensitive diabetes insipidus**. This rare disorder results from failure of the renal tubules to respond to vasopressin or to absorb water normally. It affects only males. Etiology includes hypokalemia and hypocalcemia. Manifestations, which begin soon after birth, include polyuria, polydipsia, dehydration and hyperelectrolytemia, vomiting, constipation, anorexia and failure to thrive. Management consists in offering water at frequent intervals and giving low sodium milk to the infant to prevent occurrence of dehydration and hyperelectrolytemia (hypernatremia in particular). Chlorothiazide and its derivatives are of value in reducing the urinary output.

740 Diencephalic Syndrome

It may present as:

- **Frolich syndrome** which is characterized by obesity, short stature, hypogonadism and diabetes insipidus.
- **Laurence-Moon-Biedl syndrome** which is characterized by obesity, short stature, hypogonadism, mental retardation, polydactyly and retinitis pigmentosa. It is principally a disease of males.
- **Cerebral gigantism** which is characterized by very rapid growth (linear), low IQ, awkward gait, large skull, antimongoloid slant and high-arched palate.
- **McCune-Albright syndrome** which is characterized by skin pigmentation, precocious puberty, advanced bone age and osseous rarefaction causing fractures.
- **Syndrome of generalized lipodystrophy** which is characterized by nearly absent fat (right since birth), coarse and acromegalic facies, advanced bone age, muscular hypertrophy, cardiomegaly, hepatomegaly, pigmentary changes, hypertrichosis and eventually, diabetes mellitus.

PITUITARY AND ITS DISORDERS

Pituitary gland consists of an anterior lobe (adenohypophysis) and a posterior lobe (neurohypophysis). In between is a vestigial intermediate lobe.

Pituitary Hormones

The hormones produced by pituitary are:

- **Growth hormone:** Its deficiency causes pituitary dwarfism and rarely Frolich' syndrome. Gigantism results from its excess, manifesting itself before puberty. Hyperpituitarism after puberty leads to acromegaly.
- **Prolactin:** It is mainly concerned with initiation and maintenance of lactation. Its secretion is regulated by baby's *suckling* of the nipple.
- **Gonadotrophins:** Two gonadotrophins produced by pituitary are—(1) FSH and (2) LH. **FSH** in females causes follicular growth of the ovary. Its deficiency leads to amenorrhea and excess to precocious puberty. In males, FSH stimulates gametogenesis. **LH** in females causes luteinization and rupture of the follicles. Later, it transforms the follicles into corpora lutea. In males, LH stimulates secretion of testosterone. Deficiency of LH causes sexual infantilism and its excess the precocious puberty.
- **Thyroid-stimulating hormone or thyrotrophin:** It is responsible for stimulating secretion and release of thyroxine. Deficiency of TSH causes pituitary hypothyroidism and its excess the hyperthyroidism.
- **Adrenocorticotrophin hormone or corticotrophin:** It is responsible for stimulating secretion and release of corticoids. Its deficiency, if absolute, kills the patient in short time. Relative deficiency causes hypotension, hypoglycemia, weight loss and unconsciousness in a child who has retardation of growth and sexual infantilism. Excess of ACTH leads to Cushing syndrome.

Regulation and Metabolism of Hormones

A unique feedback system, operating at the level of hypothalamic-pituitary axis as also at the level of individual endocrine glands, includes:

- Regulatory hormones
- Hormonal levels
- Hormone effects.

GROWTH HORMONE DEFICIENCY

Etiology

Growth hormone deficiency (GHD) may be congenital (genetic and developmental defects) or acquired (tumors, vascular, infective, irradiation, infiltration, traumatic, autoimmune). Box 39.1 lists causes of GHD.

Clinical Features

- GHD may manifest with severe hypoglycemic seizures (though growth is normal) in a newborn. This is because of concomitant ACTH deficiency rather than GH as such.
- It is around 1-year of age that growth retardation becomes apparent.
- Short stature with normal body proportions is the cornerstone of GHD (Fig. 39.1). Height age falls short of chronological age as well as bone age.
- Remaining features include doll-like round facies, frontal bossing, midfacial crowding, depressed nasal bridge, prominent philtrum, central obesity with high subcutaneous adiposity, and single central incisor.

Box 39.1 Causes of growth hormone deficiency

Congenital defects

• Genetic

- **Isolated deficiency:** Type I—Autosomal recessive, Type II—Autosomal dominant. Type III—X-linked recessive
- **Multiple pituitary deficiencies:** Type I—Autosomal recessive. Type II: X-linked.

• Developmental

- Aplasia
- Hypoplasia
- Anencephaly
- Holoprosencephaly
- Midfacial anomalies

• Idiopathic

- GH releasing hormone deficiency

Acquired defects

- Intracranial tumors
- IUGR
- Infections
 - **Intrauterine:** Toxoplasmosis
 - **Acquired:** Meningoencephalitis, meningitis
- Infiltration
 - Histiocytosis
 - Sarcoidosis
 - Hemochromatosis
- Vascular
 - Infarction, aneurysm
- Trauma
 - Birth injury, head injury, surgical insult
- Irradiation
- Autoimmune.



Fig. 39.1: Growth hormone deficiency. Note the gross short stature (compared with control of about same age) with doll-like round faces, frontal bossing, depressed nasal bridge, prominent philtrum and central obesity.

- Delayed sexual development (small penis and scrotum) is due to concomitant gonadotropin deficiency.
- Bone age is delayed (retarded).

Diagnosis

It is based on the following criteria:

- Height age <chronologic age (<3rd percentile).
- Bone age <chronologic age.
- Growth velocity <4 cm/year during prepubertal period.
- Maximum GH after a provocative/stimulation test <10 ng/mL.
- Abnormal GH secretory pattern.
- Reduced somatomedin C or insulin-like growth factor-1 (IGF-1) and IGFBP-3 levels.
- Normal growth resumption following GH administration.

Differential Diagnosis

Growth hormone deficiency induced short stature (SS) needs to be differentiated from other causes of short stature especially constitutional SS, familial SS, hypothyroidism, primary and secondary chronic malnutrition (nutritional dwarfing), Turner syndrome and GH insensitivity (Laron syndrome).

In Laron syndrome (in which clinical features have a striking resemblance to those in GH deficiency), GH levels are elevated. Children provisionally diagnosed as GH deficiency but not responding to GH therapy should be evaluated for this syndrome of GH insensitivity.

Treatment

In an established case of GHD, recombinant GH is administered in a dose of 0.07–0.1 IU/kg/day subcutaneous (SC) until appropriate growth is attained. For more details, See Chapter 4 (Growth Disorders). Associate

deficiencies of other pituitary hormones too need to be treated concurrently.

GROWTH HORMONE EXCESS

Growth hormone excess causes:

- **Gigantism** when excess occurs in childhood. It is characterized by somatic overgrowth. **Causes** include pituitary adenoma and McCune–Albright syndrome.
- **Acromegaly** when excess occurs after the fusion of skeletal epiphyses. Its characteristic features include—coarse appearance, prominent jaw, large tongue, broad and large nose, bushy eyebrows, dorsal kyphosis thick and rough skin. Common complaints are headache and visual defects.

Differential Diagnosis

It is mainly from cerebral gigantism (Sotos syndrome). Other differentials include Marfan syndrome, lipodystrophy, precocious puberty, obesity and tall stature.

Treatment

- Drugs—octreotide—long-acting somatostatin analog, and pegvisomant—a GH receptor antagonist.
- Surgical resection of pituitary adenoma (partial or complete) in the event of elevated intracranial pressure (ICP).

SHORT STATURE

Endocrine causes short stature include growth hormone deficiency, hypothyroidism and pseudohypoparathyroidism. For details, See Chapter 4 (Growth Disorders).

THYROID AND ITS DISORDERS

Thyroid synthesizes and secretes thyroid hormone under the influence of TSH which itself is controlled by thyrotropin-releasing hormone (TRH) of hypothalamus—three physiologically active hormones. These are thyroxine (T_4), triiodothyronine (T_3) and calcitonin. The so-called **feedback mechanism** also operates.

Thyroid hormones are primarily concerned in maintenance of growth, metabolism and mental development. Thyroid deficiency results in **hypothyroidism** which may be congenital (cretinism) or acquired (juvenile hypothyroidism). Box 39.2 gives etiologic classification of hypothyroid states. **Hyperthyroidism**, in the form of thyrotoxicosis, is rare in pediatric practice. **Nodule** of the thyroid gland is uncommon but has 50% chances of being malignant. It is always an indication for an excision biopsy. Assessment of thyroid function is by the following tests:

- **T_3 :** It is not quite dependable since it gets converted to T_4 .
- **T_4 :** More dependable than T_3 as an index of thyroid function. Free T_4 , when there is low points to the central hypothyroidism.
- **TSH:** Most sensitive. High levels points to primary hypothyroidism. Low TSH levels suggest central hypothyroidism.

Box 39.2 Etiologic classification of hypothyroidism

- Inborn defect in synthesis of thyroxine
 - Defect of iodine transport
 - Defect in iodinating tyrosine
 - Defect in production, storage and release of thyroglobulin
 - Defect in transport of thyroxine
 - Defect in utilization of thyroxine
- Thyroid tissue deficiency
 - Congenital absence
 - Congenital hypoplasia
 - Destruction from thyroiditis, surgery or irradiation
 - Antithyroid antibodies.
- Antithyroid medication during pregnancy
- Iodine deficiency (Endemic cretinism)
- Pituitary disease causing destruction of TSH
- Hypothalamic disease causing destruction of TRH.

Persistently high TSH with normal T_4 levels suggest subclinical hypothyroidism. High T_4 and negligible or undetectable TSH levels point to hyperthyroidism.

HYPOTHYROIDISM

Both congenital and acquired hypothyroidism impact growth, development and cognition unless early and appropriate treatment is initiated.

The term, **central hypothyroidism**, denotes hypothyroidism resulting from defects in the hypothalamic-pituitary axis. Defects of the thyroid gland per se and peripheral sensitivity to thyroxine may also cause hypothyroidism.

CONGENITAL HYPOTHYROIDISM**(Cretinism)**

Congenital hypothyroidism stands supreme among the causes of preventable mental retardation.

Etiology

The most common type of hypothyroid state seen in pediatric practice throughout the world is due to absence of thyroid gland (**athyrotic cretinism**), rudimentary thyroid or dysgenesis of thyroid. It is also referred to as **sporadic cretinism**. In endemic areas, it is the iodine deficiency that is responsible for congenital hypothyroidism.

Clinical Features

- The earliest manifestations include lethargy, sluggishness, hoarse cry, feeding difficulties, oversleeping, persistent constipation, prolongation of physiologic jaundice, abdominal distention with umbilical hernia, anemia (poorly responding to hematinics) and cold, dry, rough and thick skin. These infants are unusually large and heavy at birth.
- The classical features takes a few weeks (8–12) to manifest (Figs 39.2A to D). The facies characteristics—a large tongue* protruding from large open mouth

with thick lips, **puffy eyelids**, depressed nasal bridge, seemingly widely-apart eyes (**pseudohypertelorism**) and wrinkled forehead with sparse eyebrows and the hairline reaching to exceedingly low level over it.

The neck is short and there is often a pad of supraclavicular fat. The scalp hair is scanty, rough, dry and brittle. The skin is rough, thick, dry and cold. Anterior fontanel and coronal sutures are often widely open. Voice is hoarse. Dentition is delayed. Hypotonia is more or less always present.

Rarely, hypertonia with muscular hypertrophy (Figs 39.3A and B) may occur as in **Kocher-Debre-Semelaigne (KDS) syndrome**. Abdomen is often distended and an umbilical hernia of variable size is present. Hands are broad with short fingers. Anemia is generally present. Constipation, not responding to courses of laxatives, and changes in feeding regimens, is usual.

Besides the classical features, which should always arouse suspicion of congenital hypothyroidism, these children are very sluggish in their behavior. Mental retardation is invariably coexisting. Physical milestones are also considerably delayed. Growth is remarkably retarded. The upper segment/lower segment body ratio may continue to be 1.7:1, the so-called **infantile skeletal proportions**.

Investigations

It is most useful

- **Plasma:** TSH levels are high.
- **T_3 and T_4** levels are always decreased. Today, this is considered the most reliable diagnostic investigation for cretinism.
- **Radioactive iodine (I^{131})** is usually reduced.
- X-ray studies for bone age and presence of **epiphyseal dysgenesis**. The latter is seen as numerous fragmented foci of ossification, mostly in the head of femur (Fig. 39.4) and at times, in the head of humerus. Also, See Chapter 3 (Normal Growth) for various ossification centers present at birth.

Supportive

- Blood sugar (both fasting and postprandial)
- Serum cholesterol is usually elevated, especially in children beyond the age of 2 years. Here it is important to mention that normal blood cholesterol levels in infancy and early childhood are far less than the adult figures (neonates 50–100 mg/dL, infants 100–125 mg/dL, 1–5 years 150–200 mg/dL)
- Serum alkaline phosphatase is low
- Serum carotene is raised
- Electrocardiogram (ECG) is often of low voltage
- Basal metabolic rate (BMR) is low, but neither very practical nor quite helpful
- Protein-bound iodine (PBI) is usually below 2 μ g and is again not of dependable value
- Antithyroid antibodies against thyroid peroxidase and thyroglobulin.

* Other causes of macroglossia include physiological, mucopolysaccharidosis (MPS), amyloidosis, glycogen-storage disease, Beckwith syndrome, congenital arteriovenous fistula, local lymphangioma or rhabdomyoma and angioneurotic edema.



Figs 39.2A to D: Congenital hypothyroidism. (A) Note the characteristic facial features. The infant's mother had been on antithyroid drugs for thyrotoxicosis during pregnancy; (B) Note the facial features, including the large myxomatous tongue in a 10-month-old infant in whom treatment with thyroxine was initiated at the age of 8 months; (C) Profile of a 6-year-old child with untreated congenital hypothyroidism. Note mental retardation, coarse, ugly features with large protruding tongue; (D) Note the characteristic facial features and infantile proportions.

Neonatal screening for hypothyroidism consists in identifying neonates with low T_4 levels and high TSH by immunoassay methods employing cord blood on a filter paper. This observation is confirmed on a recall T_4 and TSH assay, thereby establishing the diagnosis of primary hypothyroidism. In case, T_4 level is low and TSH also turns out to be low, the infant is further investigated for thyroid-binding capacity, globulin deficiency or secondary hypothyroidism.

In the absence of adequate screening facilities, **hypothyroid index** may be of help in congenital hypothyroidism in newborns and early infancy (Table 39.1). An index of over 4 should arouse suspicion.

Differential Diagnosis

Most of the clinical features of hypothyroidism cretinism are also seen, individually or in certain combinations, in

some other conditions. Differences between **cretinism** and **mongolism (Down syndrome)** have already been tabulated in Chapter 28 (Pediatric Neurology)

Pituitary dwarfism, though stressed in the some texts as a frequent differential diagnosis, rarely causes any difficulty in pediatric practice. A pituitary dwarf is proportionally stunted in stature but is mentally fairly sound and does not have the characteristic facial and other features of cretinism.

The most common type of mucopolysaccharidosis (MPS) i.e. MPS-I (also called **gargoylism or Hurler syndrome**), has mental and growth retardation as also grotesque-like rough facial and other features resembling cretinism. But, the presence of corneal cloudiness, deformities of spine, hepatosplenomegaly and certain investigative findings in MPS-I are helpful in differentiating the two.



Figs 39.3A and B: Kocher-Debre-Semelaigne (KDS) syndrome. (A) Note the calf muscular hypertrophy in a 4-year-old child; (B) Note the remarkable hypertrophy of calf muscles.

Treatment

The **replacement therapy** with thyroid must be started as soon as possible after diagnosis, if mental retardation is to be checked. Ideally, it should begin soon after birth. Hence, the importance of recognizing the condition is in the first weeks of life. The drug of choice at present is synthetic levothyroxine (Eltroxin). Its dose is 5–10 µg/kg/day in case of patients beyond one year of age and 10–15 µg/kg/day in case of neonates and infants. Triiodothyronine is generally not recommended in treatment of cretinism. Its use is restricted to myxedema cases. Some workers, however, claim that, if it is used in the initial stage of therapy, its rapidity of action may be of advantage. Its 100 µg is equivalent to 60 mg of dessicated thyroid.

Adequacy of replacement therapy is indicated by return of activity, control of constipation, the skin



Fig. 39.4: Congenital hypothyroidism. Note the epiphyseal dysgenesis of the head of femur. Epiphyseal margin is irregular and fluffy. Substance is fragmented.

Table 39.1: Hypothyroid index

Clinical features	Scores
Feeding difficulty	1
Dry skin	1
Hypotonia	1
Open posterior fontanel (more than 0.5 cm in diameter)	1
Constipation (one stool or less/day)	1
Large tongue	3
Inactivity	3
Skin mottling	3
Edematous face	3
Umbilical hernia (more than 0.5 cm in diameter)	3

Note: A score of over 4 should arouse suspicion of hypothyroidism.

becoming warm, correction of feeding problem, improvement in appetite and improvement in PBI or T_3 and T_4 levels.

Overdosage is indicated by diarrhea, restlessness, excitability, sleeplessness, pain abdomen, vomiting polyuria, tremors and iatrogenic hyperthyroidism. Prolonged over-treatment may cause craniosynostosis. In such a situation, the dose should be readjusted. As far as possible, any interruptions in treatment should be avoided. Replacement therapy needs to be continued throughout life.

Prognosis

No replacement therapy decidedly means gross mental as well as physical retardation and risks of death from superadded infections. If adequate replacement therapy is initiated in the first 6 months of life, outlook for physical growth is fairly gratifying. About 50% of such cretins can also accomplish an IQ of 90 or even more.

ACQUIRED HYPOTHYROIDISM

Acquired hypothyroidism, unlike congenital hypothyroidism, is usually characterized by sheer subtle manifestations, often growth retardation leading to short stature.

Etiology

Late-onset hypothyroidism, results from varied causes. Most common cause of **primary hypoparathyroidism** is autoimmune thyroiditis which may be associated with other autoimmune endocrinopathies (adrenal insufficiency, diabetes mellitus, hypoparathyroidism). **Secondary hypoparathyroidism** is usually a result of combined hypothalamic-pituitary defects (injury, tumors).

Clinical Features

- Growth retardation (at times, short stature may be the only presenting feature) with absence of gross mental retardation
- Stocky appearance with large head, increased upper/lower segment ratio
- Myxedematous skin with cold intolerance
- Myopathy (hypertrophy with hypotonia)
- Pseudotumor cerebri
- Delayed dentition
- Delayed puberty
- Goiter
- Poor school performance
- Rarely, precocious puberty or hypertonia with muscular hypertrophy may be encountered
- Delayed skeletal maturation i.e. retarded bone age.

Syndromes which have enhanced vulnerability for acquired hypothyroidism include Down syndrome, Turner syndrome, celiac disease and type I diabetes mellitus.

Diagnosis

Apart from clinical evaluation, T_3 , T_4 and TSH should be done in all cases. In suspected acquired primary hypothyroidism, antibodies to thyroid peroxidase (anti-TPO) need estimation.

Treatment

Replacement therapy with l-thyroxine, 100 $\mu\text{g}/\text{m}^2/\text{day}$. To begin 25–50% of this dose should be given. Every 3–4 weeks, it should be increased by increments so as to finally arrive at the recommended dose.

HYPERTHYROIDISM

(Juvenile Graves' Disease)

Etiology

This disorder of excessive secretion of thyroid hormone, though rare in pediatric practice, may occur in fetal life and in neonates with history of maternal thyrotoxicosis. Usually, subjects are preadolescent or adolescents, with predominance of girls. Familial occurrence is on record.

Transient neonatal thyrotoxicosis may occur following transplacental transfer of maternal thyroid-stimulating immunoglobulin.

Clinical Features

- Hyperexcitability, excessive irritability, motor hyperactivity, emotional disturbances



Fig. 39.5: Hyperthyroidism. Note the exophthalmos in the young girl whose main complaint was weight loss despite good dietary intake and palpitations.

- Weight loss despite voracious appetite
- Palpitations
- Tall stature
- Exophthalmos (Fig. 39.5)
- Progressive cardiomegaly and cardiac insufficiency may incapacitate the patient.

Diagnosis

Investigations include:

- Radiological examination for bone age which is usually advanced for the age
- High serum T_4 and free T_4 and T_3 , oversuppressed TSH
- Increased uptake of radioactive iodine.

Treatment

- Methimazole, 0.5–1 mg/kg/day, is the drug of choice for pediatric hyperthyroidism.
- Propranolol, 2 mg/kg/day in 2 divided doses, to control autonomic symptoms.
- Lugol iodine and iodinated contrast assist in providing symptomatic relief.
- Prednisolone, 1–2 mg/kg/day, is of value in hyperthyroid storm.
- Digoxin for heart failure not responding to aforesaid measures.
- Radioiodine (I^{131}) for Graves' disease.
- Surgery (subtotal or total thyroidectomy) is indicated in large or toxic goiter.

GOITER

(Thyromegaly)

An enlargement of thyroid gland (lateral lobe of the thyroid gland larger than terminal phalanx of child's thumb), results from high production of TSH.

Etiology

It is generally secondary to low levels of thyroid hormone in the blood stream. It may be **congenital** or **acquired**. Both sporadic and endemic forms are known. **Endemic goiter** is due to poor intake of iodine in water and food and is

746 common in Himalayan mountains. **Sporadic goiter** results from failure to organify iodide. It is usually associated with congenital deafness, the so-called **Pendred syndrome**. The disorder has autosomal recessive transmission.

Congenital goiter may result from ingestion of goitrogenous (antithyroid) agents during pregnancy, or in association with cretinism due to inborn errors of thyroxine synthesis.

An outstanding example of acquired goiter is **Hashimoto thyroiditis** (autoimmune thyroiditis, lymphocytic thyroiditis). It is said to be the most common cause of childhood goiter in nonendemic areas. It is more often seen in girls and may, at times, be familial. Some patients with this goiter may progress to hypothyroid state. **Treatment**, if any, is thyroxine. Iodine therapy is more or less contraindicated.

Diagnosis

Over above, a good clinical examination to determine the characteristics of the thyroid swelling that may suggest the probable etiology, thyroid function tests are needed (Fig. 39.6). Remaining tests include:

- Anti-TPO antibodies
- Ultrasonography
- Fine needle aspiration cytology (FNAC).

Treatment

It is directed at the cause:

- Goiter associated with Graves' disease needs to be treated with antithyroid medication. Goiter associated with hypothyroidism should be treated with l-thyroxine.
- Physiological goiter needs to be treated with thyroxine, 100–200 µg, for a couple of years.
- Massive goiter with respiratory embarrassment is an indication for surgery.



Fig. 39.6: Goiter. Note the swelling in the neck.

Also See Chapter 11 (Nutritional Requirements) and Chapter 15 (Micronutrients/Trace Elements/Minerals) for iodine deficiency and staging of thyroid size by palpation, respectively.

PARATHYROID AND ITS DISORDERS

These glands produce a hormone, **parathormone**, which is responsible for maintenance of calcium metabolism. It mobilizes calcium and phosphorus from bone. Secondly, it reduces serum phosphate by inhibiting renal tubular reabsorption of phosphate. Thirdly, it boosts reabsorption of calcium. Fourthly, it increases reabsorption of calcium from bones. Fifthly, it increases absorption of calcium from gut.

Hypoparathyroidism may result from congenital absence (aplasia) of parathyroids. When in association with aplasia of thymus, congenital defects of central nervous system (CNS), cardiovascular system (CVS) and eye, it is termed **DiGeorge syndrome**.

Transient hypoparathyroidism may occur in newborns with hypocalcemia as a result of intake of milk of high phosphate/calcium ratio, low birth-weight infants, babies of diabetic mothers and babies born to mothers with functioning adenoma of parathyroids. The baby with transient hypoparathyroidism may have latent or overt tetany and even convulsions. Serum calcium is low.

Autoimmune hypoparathyroidism is usually seen in association with Addison disease, pernicious anemia, lymphocytic thyroiditis, persistent moniliasis, alopecia areata and steatorrhea. **Pseudohypoparathyroidism** is, on the contrary, an error of end-organ response. Parathyroid secretion is good enough. These patients are mentally retarded and have poor bone growth with short fingers and toes.

Hyperparathyroidism is a very uncommon disorder. It is characterized by hypercalcemia, hypophosphatemia and hypercalciuria. Extensive demineralization of bones is evident in X-rays. Another important cause of hypercalcemia is vitamin D intoxication.

HYPOCALCEMIA

Definition

It is defined as total blood calcium level <8 mg/dL and ionic calcium level <1.1 mmol/L. This disorder is rare in childhood.

Etiology

Box 39.3 lists etiology of hypocalcemia.

Box 39.3 Etiology of hypocalcemia

- **PTH related:** Hypoparathyroidism (autoimmune, DiGeorge syndrome) (Fig. 39.8)
- **PTH resistance:** Pseudohypoparathyroidism (Albright hereditary osteodystrophy)
- **Vitamin D-related:** Vitamin D deficiency (vitamin D deficiency/nutritional rickets), enhanced inactivation of vitamin D (AED-induced rickets), calcitriol resistance (vitamin-D dependent rickets type II), decrease action of 1α-hydroxylase action (vitamin D dependent rickets type I, renal insufficiency)

Abbreviations: PTH, parathyroid hormone; AED, antiepileptic drugs.



Fig. 39.7: Carpopedal spasm in hypocalcemic tetany. Note the spasmodic contraction of the muscles of the hands.

Clinical Features

Manifestations vary with the age group.

- **Newborn seizures:** Jitteriness, lethargy, feeding refusal.
- **Infancy and childhood:** Tetany manifesting as carpopedal spasm (Fig. 39.7).
- **Chvostek sign:** Tapping of facial nerve at an angle of jaw causes contraction of facial muscles.
- **Trousseau sign:** Inflating blood pressure cuff >systolic pressure for >5 minutes causes spasm of muscle of hand.
- **Others:** Seizures, unexplained stridor, dilated cardiomyopathy.

Diagnosis

Besides clinical features and low blood level of calcium, ECG should be done for prolonged QT interval.

Treatment

IV calcium gluconate, 2 mL/kg over 5–10 minutes.

Ionic calcium = Total calcium – $0.8 \times (\text{Albumin G/Dl} - 4)$

HYPERCALCEMIA

Hypercalcemia, a rare entity in pediatric practice, is defined as serum calcium level >11 mg/dL.

Etiology

A number of conditions can cause hypercalcemia though in children hyperparathyroidism is the most common cause (Box 39.4).

Clinical Features

- Nausea, vomiting, constipation, anorexia, muscular weakness
- Polydipsia and polyuria
- Failure to thrive, poor feeding, hypotonia and seizures in infants
- Bony deformities and pathological fractures.

Investigations

- Serum calcium levels (both total and ionized) are elevated



Fig. 39.8: DiGeorge syndrome. Note hypoplastic alae nasi with squaring of nasal tip, short philtrum, cupid bow-shaped upper lip and periorbital fullness. This is the most common cause of permanent hypoparathyroidism.

Box 39.4 Causes of hypercalcemia

- **Hypervitaminosis D:** Frequent iatrogenic massive doses.
- **Hyperparathyroidism:** Supravalvular aortic stenosis with characteristic facies (William syndrome), hypophosphatasia.
- Enhanced bone resorption from hyperparathyroidism (most common).
- Prolonged immobilization.
- **Granulomatous diseases:** Tuberculosis, sarcoidosis. Mechanism—enhanced 1-alpha hydroxylase activity.
- Malignancy.

- Serum phosphate low
- PTH elevated
- Imaging: Ectopic calcifications in skin, kidneys and basal ganglia, pathological fractures.

Treatment

- Frusemide preceded by high fluid intake.
- Antiresorptive drugs and biphosphates if no response to frusemide.
- Hemodialysis in case of poor response.
- Prednisolone for 3 weeks in
 - Iatrogenic hypercalcemia (hypervitaminosis D)
 - Elevated 1-alpha hydroxylase action.

ADRENAL AND ITS DISORDERS

Fundamentals

Adrenal cortex secretes over 30 hormonal substances, the steroid compounds. Their main functions are:

- Maintenance of electrolyte balance
- Maintenance of carbohydrate and protein metabolism
- Maintenance of growth and development
- Stimulation of sexual development.

748 *Adrenal medula* secretes catecholamines—the adrenaline and noradrenaline. **Adrenaline** raises systolic blood pressure. **Noradrenaline** increases both systolic and diastolic blood pressures. Secondly, adrenaline increases both heart rate and output whereas noradrenaline affects heart rate alone. Thirdly, adrenaline reduces coronary flow and peripheral resistance whereas noradrenaline does the reverse.

ADRENAL INSUFFICIENCY

It may result from:

- Suppression of the gland activity from prolonged administration of steroids in disorders such as rheumatic carditis, nephrotic syndrome or idiopathic thrombocytopenic purpura
- Adrenal hemorrhage
- Adrenal necrosis in fulminant infections like septicemia or meningococemia (Waterhouse-Friderichsen syndrome)
- Chronic failure of the adrenals—Addison disease—from tuberculosis or as an autoimmune process.

ADDISON DISEASE

Addison disease, rare in pediatric practice (seldom seen in infancy), is the result of autoimmune adrenal dysfunction.

Clinical Features

- Hyperpigmentation of skin (Fig. 39.9), more so on sun-exposed areas like palmar creases and elbows plus areas that are normally too hyperpigmented like areola and external genitalia, and buccal mucosa
- Hypotension
- Hypoglycemia
- Anorexia
- Weakness are its important presenting features.

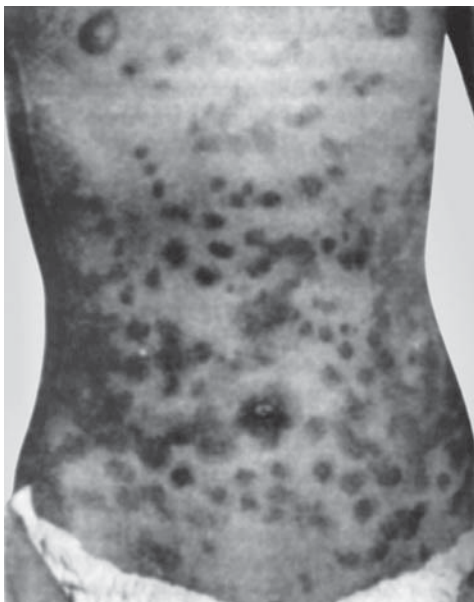


Fig 39.9: Addison disease. Note the classical hyperpigmentation in Addison disease.

Diagnosis

It is by ACTH stimulation test. Serum electrolytes and blood sugar should also be done.

Treatment

The disease responds to low doses of glucocorticoids and mineralocorticoids lifelong. In case of a salt-wasting crisis, it is important to administer hydrocortisone, 50 mg/m² stat followed by addition 4 doses of 25 mg/m² each. It is important to correct shock by fluid boluses.

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Definition

A group of inherited defects of synthesis of adrenal steroids (cortisol), resulting from deficiency of one of the enzymes essential for production of steroids. CAH is a huge mimicker because of its heterogenous and varied presentations.

Pathophysiology

Figures 39.10A and B depict the adrenal biosynthetic pathway and the blocks in this pathway responsible for CAH.

Classification

Box 39.5 gives a classification of CAH.

Clinical Features

- **CAH due to 21-hydroxylase deficiency:** Most important feature is virilization (Fig. 39.11) due to exposure to oversecreted adrenal androgens at the critical period of sex differentiation during fetal life. It may manifest as salt-losing form of CAH with severe vomiting and shock (vascular collapse), a life-threatening emergency. This is because of accompanying aldosterone deficiency. Late-onset 21-hydroxylase deficiency CAH may manifest with menstrual irregularities, hirsutism and acne later in life.
- **CAH due to 11-beta-hydroxylase deficiency:** Most important feature of this variety too is virilization. Because of accumulation of deoxycortisol (DOC), hypertension develops sooner or later.
- **Rarer types of CAH** include over 7 variants due to blocks at other levels.

Prenatal Diagnosis

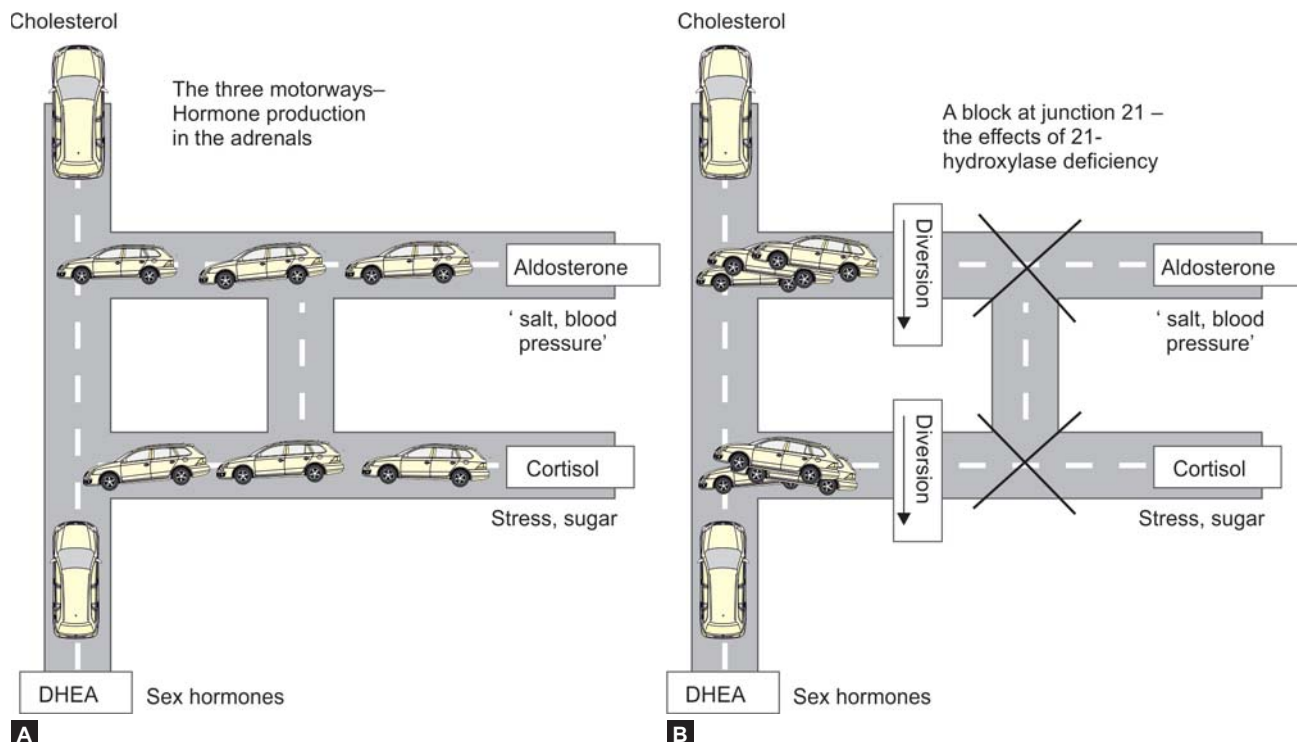
By assay of 17-ketosteroids, pregnanetriol and 17-hydroxyprogesterone (17-OHP) in amniotic fluid, by genotyping or human leukocyte antigen (HLA) typing of amniotic cells obtained by chorionic villus sampling.

Neonatal Screening

By 17-OHP assay in blood from heel-prick.

Treatment

- **Prenatal:** Dexamethasone at 5th gestational week and later.
- **Postnatal:** Glucocorticoids, increased salt intake, surgical correction.



Figs 39.10A and B: Adrenal biosynthetic pathway. Note the block in the pathway.

Abbreviation: DHEA, Dehydroepiandrosterone.

Box 39.5 Classification of congenital adrenal hyperplasia

Common form

- 21-alpha hydroxylase enzyme deficiency
- Salt-wasting
- Simple virilizing
- Nonclassified
- Cryptic

Rare form

- 11-beta-hydroxylase deficiency
- 3-beta-hydroxyl steroid dehydrogenase deficiency
- 17-alpha-hydroxylase deficiency
- Steroidogenic acute regulatory protein defect (StAR).

Diagnosis

Clinical

When to suspect hermaphroditism? Firstly, any male child who has a small penis, hypospadias and undescended testis deserves a check-up. Secondly, any girl with a suspicious mass in the labia majora or groin needs to be examined to ascertain if the mass could be testis.

In the history, one should trace history of fetal wastages and early neonatal deaths, the presence of intersex siblings or such other close relatives and the mode of inheritance. A history of consanguinity is of vital importance. Also, had the mother been ingesting hormones (progesterone or testosterone) during pregnancy? What was the time sequence of secondary sex characters in the child with ambiguous sex problem?

Clinical examination should confirm the presence or absence of testis (in the scrotum or inguinal canal), the degree of labioscrotal fusion, size of penis or clitoris,



Fig. 39.11: Congenital adrenal hyperplasia. Note the ambiguous genitalia with hypertrophied clitoris.

hypospadias and uterus through rectal examination. Renal as well as anal and other congenital anomalies should also be searched for. It is advisable to do a rectal examination for the presence of vaginal pouch, uterus or prostate.

Radiological

- **Plain X-ray** for bone age which is advanced in CAH, but delayed in gonadal dysgenesis and hypopituitarism.
- **Retrograde genitourethrogram** for status of urogenital sinus and other internal genital structures.
- **Noninvasive imaging** (ultrasonography, computed tomograph (CT) scan, magnetic resonance imaging (MRI) for status of internal genitalia, undescended gonads and anomalies of adrenal glands.

Laboratory

- **Buccal smear/peripheral blood or bone marrow karyotyping:** It is a mirror of the real gonadal sex rather than the external sex. In true hermaphrodites and female pseudohermaphrodites, nuclear sex chromatin is positive. A negative buccal smear occurs in male hermaphrodites.

- 750 ■ 17-Ketosteroids and pregnantriol:** Urinary excretion of these substances is increased in androgen-induced pseudohermaphroditism, the so-called CAH.
- **Serum electrolytes:** These may be of value in identifying salt-losing variety of CAH. High serum potassium in a child with ambiguous external genitalia, positive buccal smear and advanced bone age (especially when there is high excretion of 17-ketosteroids and pregnantriol in urine) nearly confirm this diagnosis. It is an emergency.
 - **Chromosomal studies:** Only in an occasional case such an analysis may be needed. Its indication will only be when buccal smear suggests some abnormality.
 - **Urethroscopy, vaginogram, intravenous pyelogram (IVP):** These may be of help in difficult cases to identify vagina, uterus and anomalies of the urinary tract.
 - **Gonadal biopsy:** Bilateral gonadal biopsy is a *must* when gonads are in the abdomen. In vague situations, a biopsy may be of value even though these are present externally.
 - **Laparotomy:** This may be necessary in many instances to be certain of the diagnosis.

Treatment

Early diagnosis and rearing of the child accordingly are vital. Administration of corticosteroids (hydrocortisone 20–25 mg/m²/24 hours, prednisolone 0.5 mg/kg/24 hours, in 2 divided doses) and early correction of external genitalia (feminizing genitoplasty in first year, vaginoplasty if needed at adolescence or later) give gratifying results in CAH. During infection/surgery, dose of steroids should be increased 2–3 fold. In salt-losing CAH, 4–8 g of sodium chloride should be given in first 24 hours in case of development of dehydration, preferably with 9- α -fluoro cortisone acetate (0.05–0.1 mg/day).

ADRENAL HYPERFUNCTION

- Adrenal hyperactivity (hyperadrenocorticism) causes:
 - Cushing's syndrome in case of cortisol-secreting lesions.
 - Adrenogenital syndrome from androgen-producing lesions such as adrenal tumors or adrenal hyperplasia, and rarely
 - Hyperaldosteronism.
- Adrenal medullary disorders include:
 - A rare adrenaline-secreting tumor, *pheochromocytoma*.
 - A relatively common malignant tumor, *neuroblastoma*.
 - A benign growth, *ganglioneuroma*.

Cushing's Syndrome*

Definition

It is the most common cause of adrenocortical hyperfunction, is characterized by central obesity with moon facies, buffalo hump, and striae—features that are infrequent in pediatric subjects.

Etiology

- **Exogenous steroids:** Chronic therapy with steroids, say glucocorticoids or ACTH (nephrotic syndrome, immune thrombocytopenic purpura {ITP}) is the most common cause of Cushing's syndrome in children.
- **Endogenous steroid production:** Increased adrenal glucocorticoid production in relation with increased ACTH levels or autonomous adrenal hyperfunction. In young children, chances of an adrenal pathology are high. After puberty, pituitary causes are more likely.

Clinical Features

- As a rule, onset of Cushing's syndrome is insidious.
- Growth failure (or deceleration) in height, velocity associated with accelerated weight gain is a hallmark feature of Cushing's syndrome in children.
- Other sign and symptoms often seen in children and adolescents with Cushing syndrome include facial plethora, round face (moon face), increased fine downy hair on the face, body and extremities (hypertrichosis/hirsutism), temporal fat pad, bruising (Fig. 39.12), stretch marks on abdomen, thighs, buttocks, arms, and breast, bone and muscle weakness, severe fatigue.
- Obesity in upper body with thin extremities, hypertension, diabetes mellitus, delayed puberty, pseudotumor cerebri, hypokalemia, slipped capital femoral epiphysis, are some other features.

Diagnosis

In a clinically diagnosed case of Cushing's syndrome, certain investigations are needed (Box 39.6).

Treatment

Medical therapy is in the form of inhibitors of steroidogenesis i.e. ketoconazole, cyproheptadine, metyrapone, mitotane, aminoglutethimide. Surgical resection of the causative adrenal adenoma/carcinoma is the therapy of choice.



Fig. 39.12: Cushing's syndrome. Note the upper body obesity with moon facies.

* The term, Cushing's disease, denotes hypercortisolism secondary to an ACTH-producing pituitary tumor.

Box 39.6 Recommended investigations in Cushing syndrome

Screening tests

- Assessment of diurnal cortisol rhythm
- Overnight dexamethasone suppression test
- 24-hour urine free cortisol
- Low dose dexamethasone suppression test

Tests targeting etiology

- Adrenocorticotrophic hormone levels
- High dose dexamethasone suppression test
- Urinary free cortisol.

Hyperaldosteronism

It is characterized by fluid and sodium retention with urinary loss of potassium.

Etiopathogenesis

- **Primary hyperaldosteronism** is caused by adenoma or diffuse hyperplasia or a genetic disorder, glucocorticoid remediable hyperaldosteronism (GRA).
- **Secondary hyperaldosteronism** may result from renal artery stenosis, rennin-secreting tumors, nephritic syndrome, heart failure, liver dysfunction, etc.

Clinical Features

Manifestations are in relation to hypertension and hypokalemic alkalosis.

Diagnosis

Laboratory findings include high plasma renin activity, low aldosterone levels, hyperkalemia, hyponatremia, metabolic acidosis and high corticosterone levels. In some cases, hydroxycorticosterone may be remarkably elevated.

Treatment

It revolves around salt restriction and spironolactone (aldosterone antagonist) and physiological hydrocortisone replacement. In case of adrenal adenoma, surgery is strongly recommended.

Pheochromocytoma

This is a catecholamine-secreting tumor, originating from adrenal medulla or sympathetic chain.

Etiopathogenesis

Usually, it occurs in association with other tumors e.g. neurofibromatosis, von Hippel-Lindau disease, multiple endocrinal neoplasia type II, etc. As a result of excessive catecholamine production, hypertension occurs.

Clinical Features

Manifestations are related to hypertension and include headache, nausea, vomiting, palpitations and visual disturbances. Infrequently, seizure may occur.

Diagnosis

In a case of hypertension with exclusion of causes such as coarctation of aorta, renovascular disorders, diagnosis of pheochromocytoma is based on the following investigations:

- High urinary excretion of catecholamines and their derivatives

- Ultrasonography
- CT scan
- MRI
- Scintigraphy.

Treatment

Treatment of choice is surgical removal of the tumor(s) after an alpha-blockade preoperatively.

GONADS AND THEIR DEFICIENCY

Gonads, testes in males and ovaries in females, are no less important.

Testicular hypofunction or deficiency (hypogonadism): It is an important finding in the **Klinefelter syndrome** (Fig. 39.13). Such a patient has XXY chromosomal pattern with positive buccal smear, looks more of a male, is tall and may have gynecomastia. Testes are just rudimentary. Hypogonadism in males may also result from mumps, tuberculosis, syphilis, tumors, surgical removal and lack of interstitial-cell stimulating hormone (ICSH) of the pituitary gland.

In females, an important cause of ovarian dysfunction is **Turner syndrome** (Fig. 39.14) (gonadal dysgenesis). Its chromosomal pattern is XO with negative buccal smear though occasionally XO/XX pattern with negative buccal smear may also be encountered. Delayed or even absent secondary sex characters, short stature, webbing of neck, cubitus valgus and mental retardation are its important clinical features. Coarctation of aorta is present in some cases. A newborn with edema right at birth, should arouse suspicion of Turner syndrome. The patient is always a girl.

In **Noonan syndrome (male Turner)**, some of the features of true Turner syndrome are present but chromosomal pattern is normal.

UNDESCENDED TESTES

(Cryptorchidism)

In some 3 to 4% of term and 20 to 30% of preterm infants, testes may fail to descend to their normal abode, i.e. scrotum. By the time the infant is 1 year old, incidence comes down to just 1% because in most cases testes have already descended down into scrotum. After 1 year of age, such a descent seldom occurs spontaneously.

Etiology

Causes include:

- Testicular failure
- Deficient hormonal stimulation
- Mechanical obstruction
- An ectopic attachment.

Cryptorchidism may be unilateral or bilateral, the former being more common.

Types

Pseudocryptorchidism

At times, because of the cremasteric reflex, testis may be temporarily pulled up from the scrotum into the inguinal

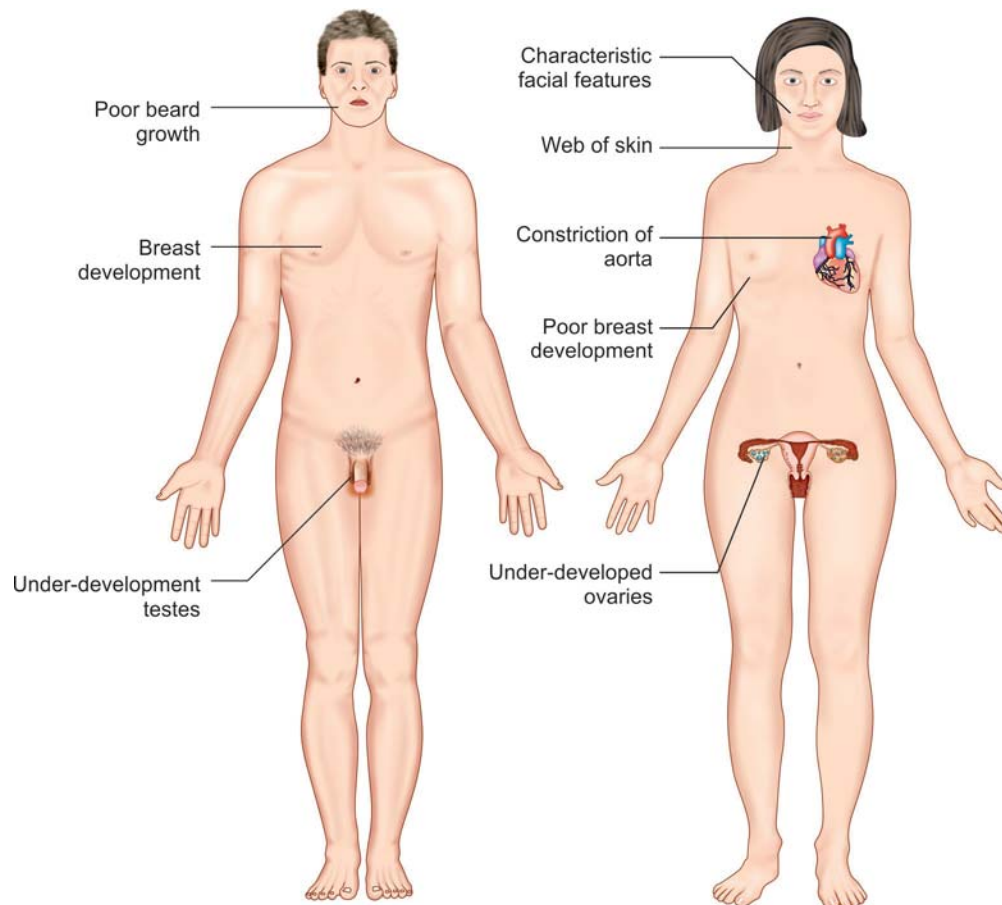


Fig. 39.13: Klinefelter syndrome. Note the presentation in an apparently male and female.

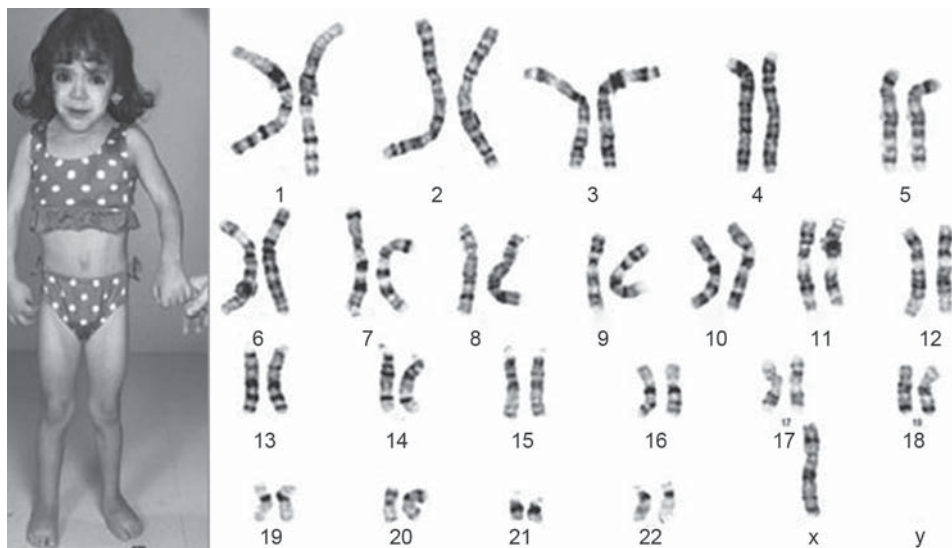


Fig. 39.14: Turner syndrome: Note the classical features and karyotyping.

canal or abdomen, especially when examination is conducted in a cold environment. Such a testis can be coaxed back into the scrotum by sliding the fingers from the internal inguinal ring towards the neck of the scrotum. Ascent into the abdomen can be prevented by placing the fingers across the upper portion of the inguinal canal. This condition is termed *retractile testis* or *pseudocryptorchidism*.

True Cryptorchidism

It is characterized by undescended testes that is located in the abdomen or inguinal canal. Rare sites of location are perineum, femoral area and front of symphysis pubis at the base of penis (ectopic testis). In true cryptorchidism, scrotum on the affected side is usually smaller. An associ-

ated inguinal hernia is frequent. In bilateral cryptorchidism, scrotum is flat.

Complications

An undescended testes is vulnerable to malignancy and poor spermatogenesis.

Treatment

Since spontaneous descent in cryptorchidism is unusual after the age of 1 year, the best time for therapy is between 1 to 2 years of age. If trial of hormonal therapy with human chorionic gonadotropin (hCG) or leuteinizing hormone-releasing hormone (LHRH) fails, surgery (orchiopexy) should be undertaken promptly by 2 years of age.

MICROPENIS

Definition

Micropenis is defined as a penis with a length at least 2 standard deviations (SD) of the mean for age (Fig. 39.15).

Etiology

Testicular failure (primary or secondary) is responsible for micropenis in most of the cases. Reduced androgen in fetal life is the root cause.

- Hypogonadotropic hypogonadism: Prader-Willi syndrome, Kallmann syndrome, Klinefelter syndrome, septo-optic dysplasia
- Partial androgen insensitivity syndrome
- Testosterone biosynthetic defects

Investigations

Gonadotropin and testosterone level estimation, if reduced, suggest hypogonadotropic hypogonadism. On the other hand, if gonadotropin levels are high, point to hypergonadotropic hypogonadism. This situation calls for further evaluation for steroidogenic abnormalities, testicular dysgenesis and androgen insensitivity syndrome.

Treatment

Early intervention in the form of a short course of low dose testosterone (25 mg once a month \times 3 months) usually contributes to attainment of normal sexual function.



Fig. 39.15: Micropenis. Note the very small penis. Both testes were, however present in this child.



Fig. 39.16: Precocious puberty. Observe the noteworthy breast enlargement, in a 7-year-old girl.

Precocious Puberty

Definition

Development of secondary sex characters, much before the anticipated age, is referred to as **precocious puberty**. The age cutoff landmark for boys is 9.5 years and for girls 8 years. Breast enlargement (Fig. 39.16), menarche, excessive enlargement of penis or clitoris, dark and coarse axillary and pubic hair, change in voice and acne rank among the various features which, if noticed in a child under 8 to 10 years, should arouse suspicion.

Types

- **True precocious puberty or central precocious puberty (CPP):**

It is characterized by premature occurrence of spermatogenesis or ovulation. The cause is premature activation of hypothalamic-pituitary axis, leading to secretion of gonadotropin and complete maturation of gonads. In most cases, it is difficult to trace the exact etiological factor operating at the level of the hypothalamic-pituitary axis (idiopathic or constitutional type). In some, it may be possible to find an operating factor like a congenital anomaly, post-meningitic or postencephalitic scar, tumor or previous trauma (secondary type).

- **Pseudoprecocious puberty or peripheral precocious puberty (PPP):**

It is characterized by premature appearance of secondary sex characters and rapid somatic growth. This results from increased levels of androgenic and estrogenic hormones. The cause is at the level of adrenals or gonads.

- **Combined central and peripheral precocious puberty:**

It comprises existence of PPP which activates the hypothalamic-pituitary axis, resulting in CPP as well.

754 Diagnosis

A good history and physical examination should be of value in forming provisional impression as to the type of precocious puberty and the possible cause(s) in a particular case. A CNS tumor or a tumor of the testes, ovaries or adrenals should be borne in mind if the well-known causes do not seem to be operating.

- X-ray studies of the skull, hands and elbows for intracranial tumors and bone age.
- Endocrinal studies in the form of:
 - Urinary 17-ketosteroids,
 - Urinary pregnanediol,
 - Vaginal smear for estrogen activity
 - Gonadotrophin FSH and LH.
- Gonadal biopsy.
- Surgical exploration of abdomen.

Treatment

As far as possible, the etiologic factor should be removed. In CPP, drug therapy is in the form of gonadotropin releasing hormone (GnRH) analogues (tritrelin, leuprolide) intramuscularly once a month.

In PPP, drug therapy consists in giving progestational agents such as medroxyprogesterone acetate, 100 mg/m² every 2-3 week IM or 10 mg twice daily (O). These agents act by suppressing gonadotrophin secretion in either sex. A relatively new drug, cyproterone, has an additional property. It is also antiandrogenic. Excellent results have been reported by its use in a dose of 75-100 mg/m² in 2-3 divided doses. Yet another effective agent in PPP is ketoconazole.

Precocious puberty—in girls in particular—is accompanied by interlinked social and psychological problems. The role of counseling and sex education is vital. The subjects should be advised to behave according to their chronologic age rather than their sexual age. Further, they should be protected from adverse environmental influences. Further, they need to be protected against sexual abuse.

DELAYED PUBERTY

Definition

The term refers to the absence of signs of sexual development (increase in volume of testes in boys, breast budding in girls) by 13-14 years in girls and by 14 years in boys.

Etiology

Box 39.7 lists important causes of delayed puberty.

Diagnosis

History and clinical examination should obtain information on primary or secondary nutritional deficiencies, chronic illnesses and any family history of delayed puberty, testicular size, phallic length, pubic hair, breast development, growth velocity, etc.

Special investigations include bone age, endocrinal assessment with special reference to basal levels of sex hormones, gonadotrophins, adrenal androgens, prolactin,

Box 39.7

Etiologic factors in delayed puberty

- **Constitutional delay of growth and puberty (CDGP)**
- **Chronic systemic disorders**
Chronic/prolonged malnutrition, celiac disease, tropical sprue, cystic fibrosis, chronic anemia, anorexia nervosa
- **Hypogonadotrophic hypogonadism (failure of GnRh and/or low FSH, LH)**
 - **Congenital/genetic:** Kallmann syndrome, Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, Laurence syndrome, congenital anomalies, primary gonadotrophin deficiency (hypopituitarism)
 - **Acquired:** Intracranial tumors, inflammatory lesions and traumatic lesions, irradiation of hypothalamic-pituitary region, hypothyroidism, hyperprolactinemia
- **Hypergonadotrophic hypogonadism/primary gonadal failure (high FSH, LH)**
 - **Congenital/genetic:** Turner syndrome (45XO), Klinefelter syndrome (47XXY), Noonan syndrome
 - **Acquired:** Mumps-related orchitis, anticancer therapy for gonads, vanishing testes syndrome, testosterone biosynthetic defects, infiltrative or autoimmune diseases of gonads.

Abbreviations: GnRh, Gonadotropin-releasing hormone; FSH, follicle stimulating hormone; LH, lutenizing hormone.

GnRH stimulation and HCG stimulation tests, karyotyping, testicular biopsy in boys and pelvic ultrasonography and vaginal smear in girls.

Management

It is of the underlying cause. Hormonal therapy may be warranted to promote puberty and sustain sexual characteristics.

Hormonal Therapy in Girls

- **Age of initiation:** After 12 years
- **Recommended agent:** Low dose estrogen i.e. ethinyl estradiol 5 µg or conjugated estrogen 0.3 mg
- **Schedule:** The agent is administered daily. Every 3 months, dose is increased so that by 2 years of therapy, the maximum dose 20 mcg of ethinyl estradiol (or 1.25 mg of conjugated estrogen) is reached. At this stage (2 years after beginning of therapy) or after onset of withdrawal bleeding, medroxy-progesterone acetate (MPA), 5-10 mg, from day 11 to 21 needs to be added.

Hormonal Therapy in Boys

- **Age of initiation:** After 14 years of age and bone age of 13.5 years.
- **Recommended agent:** Testosterone enanthate, 100 mg
- **Schedule:** Three monthly injections of testosterone enanthate. Another course may be given in case of unsatisfactory response. In case response is yet not satisfactory, it is advisable to determine serum testosterone level, If levels turn out to be low, there is need for a continued therapy since the cause of delayed puberty is in all probability hypogonadotrophic hypogonadism.

DISORDERS OF SEXUAL DIFFERENTIATION

(Intersex Disorders, Ambiguous Genitalia, Hermaphroditism)

It is by no means infrequent to encounter a child with ambiguous external genitalia. These are characteristic

of neither a male nor a female. Hence, the designation *intersex or hermaphrodite**.

Types of Hermaphroditism

- **True hermaphroditism:** This condition is quite rare. Here the individual possesses both an ovary and testis, either in the same (ovotestis) or opposite gonads. Most of the subjects have 46 XX karyotype.
- **Pseudohermaphroditism:** Here the gonads are normal. The external genitalia are, however, of the opposite sex. The condition is relatively common. Two types of pseudohermaphroditism are *male* and *female*.
 - **Male pseudohermaphroditism (MPH)** is generally characterized by male phenotype. Testes may be undescended. The penis is small with hypospadias. Labioscrotal folds are fused. A casual look gives an impression of female genitalia.
 - **Female pseudohermaphroditism (FPH)**, the most common variety, is characterized by female phenotype. Ovaries are present. Clitoris is large enough and looks like a penis. It is usually secondary to excessive intake of androgens by the mother or CAH.

DIABETES MELLITUS

Childhood diabetes also referred to as *juvenile* or *growth-onset diabetes* is characterized by wide-range of metabolic abnormalities of carbohydrates, proteins and fats in the body. Today, it is the commonest endocrine-metabolic disorder of childhood and adolescence with far-reaching effects on child's physical and emotional development.

It is estimated that childhood diabetes accounts for around 5% of total population of diabetics. In India alone, there are likely to be about 4,00,000 infants and children with this disease. A WHO report places the figures at 40,000 in Bangladesh, 60,000 in Pakistan, 20,000 in Sri Lanka, 27,000 in Nepal and 5,000 in Afghanistan.

Childhood Diabetes vs Adult Diabetes

The differences between the two are given in Box 39.8.

Current Classification

Diabetes mellitus is now classified globally as Type I and Type II (Box 39.9). The major differences between the two types are summarized in Table 39.2.

Etiopathogenesis

Almost 95% of pediatric cases belong to the idiopathic category—absolute deficiency of insulin—believed to be a hereditary inborn error of metabolism. In a considerable proportion of cases, the disease runs in the family. Siblings—identical twins in particular—show higher incidence than the parents. In a much smaller category, the

Box 39.8 Childhood diabetes vs adult diabetes

- Childhood diabetes is usually rapid in onset, often first presenting as diabetic coma. Onset in case of adult diabetes is insidious.
- Unlike adult diabetes, obesity plays no role in childhood diabetes.
- Children always need injectable insulin. Most adults with diabetes respond to oral hypoglycemic agents.
- Dietetic control alone never works in diabetic children.

Box 39.9 WHO/ADA classification of diabetes mellitus

- **Type I diabetes (juvenile-onset diabetes)** is characterized by gross insulinopenia and dependence on exogenous insulin for prevention of ketoacidosis. It occurs predominantly in childhood but no age is a bar. Association with certain autoimmune processes and diseases is its outstanding features.
- **Type II diabetes** (previously termed adult-onset diabetes, maturity-onset diabetes or stable diabetes), is usually not insulin-dependent and not complicated by ketoacidosis. It is rare in children and adolescents. There is no association with autoimmune process or disease.
- **Other specific types (secondary diabetes mellitus)**
 - **Genetic defects of beta-cell function:** Mitochondrial DNA
 - **Genetic defects in insulin action:** Leprechaunism
 - **Diseases of exocrine pancreas:** Cystic fibrosis, pancreatitis, fibrocalculus pancreatopathy, surgery
 - **Endocrinopathies:** Cushing's syndrome, hyperthyroidism, acromegaly
 - **Drug/chemical induced:** Steroids, phenytoin, thiazides, diazoxide, pentamidine
 - **Infections:** Rubella virus, cytomegalovirus
 - **Immune-mediation:** Stiffman syndrome, anti-insulin receptor antibodies
 - **Other chromosomal/genetic syndromes:** Down's syndrome, Turner syndrome, Klinefelter syndrome, Laurence-Moon-Biedl syndrome, Wolfram syndrome.

Abbreviations: WHO, World Health Organization; ADA, American Diabetes Association; DNA, deoxyribonucleic acid.

disease is secondary to such causes as Cushing syndrome, hyperpituitarism and surgical removal of the pancreas. Transient diabetes of the newborn is more or less a benign condition. It disappears in 4–8 weeks period.

That genetic factors play, role in type I diabetes stands established (Table 39.3). This explains why the disease has higher incidence in some families, the concordance rates in monozygotic twins and ethnic and racial differences in prevalence. It is now believed that at least one major vulnerable locus may reside in the DQB, gene. Around 100 fold relative risk for developing type I diabetes is conferred by the homozygous absence of aspartic acid at position 57 of the HLA-DQB chain.

Autoimmune basis for development of type I diabetes in predisposed individuals has a wide support by now. The increased prevalence of the disease in individuals with Hashimoto thyroiditis, Addison disease and pernicious anemia (all resulting from an autoimmune mechanism) as also presence of islet cell antibodies (ICA) in 80 to 90% patients of diabetes strongly favors the autoimmune basis. The type I diabetes as well as the aforesaid disorders are known to be associated with an increased incidence of

* Hermes refers to the "god" and the aphrodite to the "goddess".

Table 39.2: Major differences between type I and type II diabetes

Features	Type I	Type II
Mode of onset	Acute	Slow
Age of onset (years)	<30, predominantly childhood	>30
Family history of diabetes	Around 10%	Strong
Concordance in identical twins	25-50%	100%
Role of obesity	No proven role	A remarkable predisposing factor
Association with HLA DR 3 and 4	2.5 times	Strong
Anti-islet cell antibody	>80%	<5%
Ketoacidosis	Common	Negligible
Microvascular complications	Rare	Frequently present
Insulin	A must for treatment	Infrequently needed

Table 39.3: Disorders associated with diabetes

Diseases	Genetic syndromes
<ul style="list-style-type: none"> • Cystic fibrosis, Hashimoto thyroiditis • Adrenal insufficiency • Atrophic gastritis • Vitamin B₁₂ malabsorption • Multiple endocrine deficiency syndrome • Acanthosis nigricans 	<ul style="list-style-type: none"> • Prader-Willi syndrome • Werner syndrome • Cockayne syndrome

certain HLAs that are located on chromosome 6 and are a cluster of genes. The latter code transplantation antigen, plays a major role in immune response.

In addition, certain triggering factors like mumps, rubella, coxsackievirus and, perhaps, some other viral infections play some role in inducing type I diabetes. Antecedent stress and some toxins are also implicated as triggering factors. The triggering factors may act by destroying the B cells, by persisting in cells as a slow damaging factor, or by inducing a widespread immune response.

How does insulin lack produce multiple metabolic abnormalities? Since sugar cannot enter cells, the latter utilize amino acids or fatty acids as alternate energy sources. What follows is fat and energy (protein) wasting. Acetone, acetoacetic acid and beta-hydroxybutyric acid tend to accumulate in the circulation.

Clinical Features

The onset is generally acute. Excessive thirst (polydipsia), polyuria (more marked at night (nocturia), enuresis in a child who was earlier dry, excessive hunger (polyphagia), weight loss, general weakness, tiredness and bodily pains

* Diastix (Miles India Ltd)

** Ketodiastix (Miles India Ltd)

Table 39.4: Symptoms and signs of diabetic ketoacidosis

Symptoms	Signs
Nausea	Dehydration
Vomiting	Tachycardia
Abdominal discomfort/pain	Hypotension/shock
Polyurea	Tachypnea
Polydipsia	Respiratory distress with Kussmaul breathing and fruity odor
Polyphagia	Tender abdomen
Nocturia	Raised intracranial pressure from cerebral edema
Backache	Lethargy
Shortness of breath	Change in sensorium progressing to coma
	Evidence of infection (precipitating factor)

are the earliest presenting features. "Fainting attacks" due to spontaneous hypoglycemia, vulvitis, abdomen pain, nausea and vomiting, irritability and deterioration in school performance may also occur.

Diabetic coma may well be the first manifestation forcing the parents to bring the child to the hospital in half of the pediatric cases. **Diabetic ketoacidosis** in early stage manifests by symptoms of hyperglycemia and ketoacidosis, including polyurea, polydipsia, polyphagia, nocturia, loss of weight, nausea, vomiting, abdominal pain (at times simulating pancreatitis or appendicitis), backache, and dehydration. In advanced disease, change in sensorium, increased respiratory rate with Kussmaul breathing (rapid deep breathing in an attempt to excrete excess CO₂) preceded by one or more precipitating factor (infection, trauma, intercurrent illness) are present. Untreated ketoacidosis invariably ends up in coma.

Table 39.4 lists important symptoms and signs of diabetic ketoacidosis

Diagnosis

Once pointers in the clinical profile have aroused suspicion, the diagnosis must be confirmed by certain investigations:

- **Urine examination** for sugar and acetone. Urine sugar may be detected by Benedict test or by employing the specially prepared strips* which give the result within a minute and are highly reliable. For detecting acetone in urine, ferric chloride and Rothera tests or paper strips** may be employed.
- **Fasting blood sugar** above 126 mg/dl is diagnostic, between 100-126 mg/dl is highly probable (suspicious)
- **Random blood sugar** above 200 mg/dl on two separate occasions in a clinically suspected situation strongly supports the diagnosis.
- **Glucose tolerance test**, though infrequently required, should be performed in doubtful cases, with a glucose dose of 1.75 g/kg ideal BW (maximum 75 g).

Box 39.10**WHO/National Diabetes Data Group diagnostic criteria for diabetes mellitus**

Random blood sugar (RBS) >200 mg/dL with symptoms of diabetes
OR
Fasting blood sugar (FBS) >126 mg/dL
OR
Two hour plasma glucose >200 mg/dL during an oral glucose tolerance test.

Diabetic ketoacidosis (DKA) is characterized by hyperglycemia (glucose over 250–300 mg/dl), ketonemia, acidosis (pH under 7.3 and bicarbonate under 15–20 mEq/L), glucosuria and ketonuria. It needs to be distinguished from acidosis and/or coma from other causes, say hypoglycemia, uremia, severe dehydration with metabolic acidosis, encephalitis, salicylism, etc.

Nonketotic hyperosmolar coma exists when there is profound hyperglycemia (glucose over 600 mg/dl), nil or slight ketosis, nonketotic acidosis, severe dehydration, and neurologic signs like seizures, positive Babinski, hyperthermia and hemiparesis. The condition is infrequent in children. Box 39.10 presents the WHO/National Diabetes Data Group diagnostic criteria for diabetes mellitus.

Management**Routine Diabetes**

Though diabetes can be managed at home, in order to achieve initial stabilization, the diabetic child should be hospitalized for some days. Various objectives of management include:

- Control of overt manifestations
- Safeguarding against progression to diabetic ketoacidosis (DKA)
- Safeguarding against development of hypoglycemia
- Ensuring good nutrition for normal growth and development
- Prevention/treatment of superadded emotional overlay
- Early detection and treatment of infection(s)
- Prevention of complications (acute, intermediate and chronic vascular).

Insulin in low dose regimen is the current recommendation. A daily dose of 0.5 unit/kg body weight of soluble insulin suffices in a large majority of the cases. This total dose should be divided into 2 parts, 2/3rd to be injected before breakfast, and 1/3rd before dinner. According to the split-mix regimen, each dose consists of 2/3rd lente (NPH) and 1/3rd regular insulin. Urine should be examined before each injection. Some patients may require increase in dose or one or two additional injections before glycosuria and ketonuria are really controlled. One must make sure that if an alteration in total dose is warranted, it is in neither over 10–15% of total dose nor over 6 units/day.

After a few days, a combination of rapidly-acting soluble insulin and delayed-acting insulin (Lente, intermediate or long acting) may be all right. It is worth noting that slight glycosuria is acceptable. In fact one should not be fussy about having too many “clear” samples of urine to minimize risk of hypoglycemia.

Box 39.11**Ideal investigative components in pediatric diabetes during follow-up**

- Self-monitoring of blood glucose, urine glucose and ketones
- Glycosylated Hb every 3 months
- Urine for proteins at each follow-up visit
- Serum lipids (cholesterol, HDL, LDL, VLDL, fractions and triglycerides once a year
- Thyroid function tests (TSH, T₄)
- Ophthalmic check-up, including fundoscopy, by an expert once a year.

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein, TSH, thyroid stimulating hormone; T₄, thyroxine.

About 3-month insulin therapy may cause such a great deal of improvement that the patient requires no more insulin for many months. It is, however, advisable to continue about 5 units of insulin during this phase of remission. This is of value in preventing insulin allergy as well as resistance when the full-dose insulin therapy is resumed on relapse. Ultralente insulins having as prolonged action as 30 hours and ability to maintain a constant blood level and a short-acting human insulin analogue are also available now. Box 39.11 lists the important investigative components in the diabetic child already on treatment.

Diabetic Ketoacidosis (DKA)

Diabetic ketoacidosis, a serious emergency, is defined as a state of the trio of “hyperglycemia, dehydration and ketotic acedemia”. In its management, immediate concern is to restore fluid volume and acid-base status to normal at the earliest rather than aim at a stable euglycemia.

- **Fluids and electrolytes:** Intravenous drip is immediately started to combat dehydration and electrolyte imbalance which are often present. Initial fluid should be isotonic saline (0.9%) and the quantity based on the assumption that dehydration in diabetic ketoacidosis is in the order of 10%. The rate should be so adjusted that only 50 to 60% of the calculated deficit is given in the first 12 hours. Rest of the 40 to 50% of the deficit therapy is given in the next 24 hours.

Potassium should be added early to the infusion (when about 20 ml/kg of isotonic saline has been given) and continued as long as drip is continued. It should be administered as potassium phosphate. If symptomatic hypocalcemia develops, it should be corrected with calcium gluconate.

Soda bicarbonate is not needed routinely. It is recommended only when pH is under 7.2. For pH 7.1–7.2, the dose is 40 mEq/; for pH under 7.1 it is 80 mEq/m². It should be infused over a 2-hour period. A bolus infusion may cause cardiac arrhythmias and is not recommended.

If raised intracranial pressure develops, life saving measures like reduction in rate of infusion, mannitol (10–20 ml/m² IV, repeated at 2 and 4 hours) and hyper-ventilation must be instituted.

- **Insulin:** Continuous low dose infusion is the most modern treatment of diabetic ketoacidosis/coma. The

Box 39.12**Monitoring during management of diabetic ketoacidosis**

- Vital signs every hourly
- Neurological signs every 1-2 hourly
- Fluid intake and output every hourly
- Blood sugar, electrolytes, pH, bicarbonate every 1-2 hourly. Later it may be done every 4 hourly
- Serum calcium, phosphorous and magnesium every 12 hourly
- Appropriate culture and chest X-ray for evidence of infection
- Obtain glycosylated Hb, lipid profile and insulin autoantibodies.

dose of soluble insulin for this purpose is 0.1 unit/kg bolus followed by 0.1 unit/kg/hour. It is added to the delivery chamber of the infusion set. The method causes fall of blood sugar at the rate of approximately 75 mg/dL every hour. The insulin infusion is required to be continued until the blood sugar falls to 250 mg%. Following fall of blood sugar <250 mg/dL, 5% glucose may be added to the drip to prevent rapid fall in blood sugar.

When blood pH has reached over 7.36 and blood glucose under 300 mg/dL, patient is usually in a position to take oral feeds. At this stage, it is appropriate to switch from IV insulin to SC insulin.

- **Monitoring:** Diabetic ketoacidosis management is incomplete without close monitoring of vital signs, level of sensorium and such investigations as blood glucose and urine ketone, electrolytes, pH and urine output all along the course of IV infusion (Box 39.12).
- It is advisable to have an initial ECG and repeat it 6-8 hourly. Serum calcium and phosphate should be done every 6-8 hourly and when IV infusion is terminated. A high index of vigilance and suspicion is vital to prevent/detect iatrogenic hypoglycemia (blood sugar <60 mg/dL; early symptoms: sweating, pallor, trembling, tachycardia, late symptoms: drowsiness, confusion, seizures and coma) and cerebral edema that may complicate overcorrection with very high doses of insulin, hyperglycemia, hyperosmolality, overuse of alkali and overhydration.
- **Antibiotics** to control superadded infection
- **Diet** with the aforesaid regimen, most children with diabetic ketoacidosis can switch on to oral fluids after 8 hours and semisolids by 12 hours. The physician should see to it that the patient leads, as far as possible, a normal life and achieves normal growth and development.

This necessitates intake of recommended requirements for age. Around 45-50% calories should come from carbohydrates (preferably complex carbohydrates like whole meal cereals, whole meal bread and pulses), 15-20% from protein and 25-30% from fats (avoid upper limit). Today, the trend is to avoid too many dietetic restrictions. Concentrated carbohydrates like candies, sugar, sweets, chocolates and cakes should, however, be avoided.

- **Parental education** The physician must discuss various aspects of child's diabetes with the child as also with parents. The exercise has got to be a continuing

Box 39.13**Common complications of pediatric diabetes mellitus**

- **Acute (usually reversible):** Diabetic coma/ketoacidosis, hypoglycemia, fulminant and hidden infections
- **Intermediate (potentially reversible):** Growth failure, delayed sexual maturation, impaired neuropsychiatric development, restricted joint mobility
- **Chronic (usually irreversible):** Secondary to macro or microvascular pathology and manifesting later in life
- **Ophthalmic retinopathy** (most frequent microvascular alteration after 2 years of age)
- **Neuropathy:** Reduced motor nerve conduction velocity, sensory changes, reduced vibration perception, peripheral neuropathy, hypoglycemic awareness due to autonomic neuropathy
- **Vascular:** Hypertension, atherosclerosis
- **Renal:** Kimmelstiel-Wilson syndrome, renal failure, overt nephropathy (urine protein >0.5 g/24 hours, albumin 0.3 g/24 hours or 200 µg/minute), microalbuminuria (urine albumin 0.03-0.3 mg/24 hours or 20-200 µg/minute)
- **Metabolic:** Cataract*
- **Hepatic** Hepatomegaly
- **Chronic infections:** Boils, styes, abscesses, fungus infection, tuberculosis
- **Dyslipidemia:** Celiac disease.

* Other causes of late-onset cataract include Down's syndrome and myotonic dystrophy.

program. This needs a good rapport between the physician on one hand and the child and the family on the other. The child and parents need to learn administration of insulin injection, blood sugar testing, recognition of warning signals of hypoglycemia, hyperglycemia, ketoacidosis, infection, etc.

Complications

These may be acute, intermediate or chronic (Box 39.13).

Prognosis

Modern treatment has revolutionized the course of diabetes mellitus. Most children with controlled disease have fairly reasonable growth and development. There is remarkable increase in the average life span. With this increase in the life expectancy, the risk of long-term complications does coexist.

THE OBESE CHILD

Obesity is defined as the excessive accumulation of fat in the subcutaneous and other body tissues and parts. Whereas in case of **overweight**, body weight is increased over 110% of the standard weight (corresponding to >30 mm triceps skinfold thickness), in obesity the increase exceeds 120% of the standard weight.

Endocrinopathies causing obesity include hypothyroidism, Cushing syndrome, hypogonadotrophic hypogonadism, pseudohypoparathyroidism (Albright syndrome), polycystic ovaries (Stein-Leventhal syndrome), Frohlich syndrome, and postencephalitic/ postmeningitic sequelae. For details, refer Chapter 4 (Growth Disorders).

Multiple Choice Questions

- Which of the following is not a characteristic feature of growth hormone deficiency?
 - Proportionate short stature
 - Bone age < height age < chronological age
 - Sexual infantilism
 - Mental retardation
- Which of the following is not a feature of hyperthyroidism?
 - Weight loss despite voracious appetite
 - Emotional disturbances
 - Palpitations
 - Lack of sweating
- Most common endocrine disorder of childhood is:
 - Congenital hypothyroidism
 - Thyrotoxicosis
 - Congenital adrenal hyperplasia
 - Type 1 diabetes mellitus
- Common nephrogenic complications of type I diabetes mellitus after 2 years include each of the following, except:
 - Kimmelstiel-Wilson syndrome
 - Renal failure
 - Retinopathy
 - Nephrotic syndrome
- Bone age is advanced in each of the following conditions, except:
 - Hyperthyroidism
 - Congenital adrenal hyperplasia
 - Hyperaldosteronism
 - Cerebral gigantism
- Epiphyseal dysgenesis is a feature of:
 - Growth hormone deficiency
 - Congenital adrenal hyperplasia
 - Hypothyroidism
 - Addison disease

Answers

1. D 2. D 3. A 4. D 5. C 6. C

Clinical Problem-solving

Review 1

A 15-year-old tall girl (height 165 cm) presents with weight loss despite good appetite and good dietary intake, palpitations and excessive sweating (even in winter) and irritability. Examination reveals exophthalmos and motor hyperactivity.

- What is the most probable clinical diagnosis?
- How will you confirm the diagnosis?
- How will you treat such a case?
- Any role of surgery?

Review 2

A 12-year-old boy presents with persistent headache, nausea, vomiting, palpitations and numerous café-au-lait spots varying from 1 cm to 5 cm in diameter. ENT and ophthalmic examinations are normal. However, his blood pressure turns out to be around 150/90 mmHg in upper as well as lower limbs.

- What is the most likely diagnosis?
- How to establish the diagnosis?
- What is treatment of choice?

contd...

Answers**Review 1**

1. Clinical profile of this adolescent girl is strongly suggestive of hyperthyroidism.
2. Thyroid profile is a must in this patient. High serum T_4 , free T_4 , T_3 low TSH, and increased uptake of radioactive iodine confirm the diagnosis. Moreover, bone age is invariably advanced.
3. The drug of choice is methimazole, 0.5–1 mg/kg/day, is the drug of choice. Additionally, propranolol is indicated for autonomic symptoms.
4. Only indication of surgery is toxic goiter or large goiter.

Review 2

1. Pheochromocytoma in view of high blood pressure (about the same in both upper and lower limbs) and normal ophthalmic and ENT examination. Presence of café-au-lait spots (suggesting diagnosis of neurofibromatosis-1) lend support to the clinical impression.
2. High urinary excretion of catecholamines and their derivatives together with ultrasonography, CT scan and MRI or scintigraphy are important in establishing the diagnosis of pheochromocytoma.
3. Surgical removal of the tumor(s) after a alpha-blockade preoperatively is the recommended treatment for pheochromocytoma.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

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BOOK/MONOGRAPH

1. Gupte S. *Recent Advances in Pediatrics (Special Vol. 13: Pediatric Endocrinology)*. New Delhi: Jaypee 2004.

DEFINITION

The term **genetics** (*gene* stands for “to become”), first coined by Bateson in 1906, implies “the branch of biological science that deals with the transmission of characters from parents to offsprings”.

THE HUMAN GENOME PROJECT (HGP)

The sequencing of the human genome is of vital assistance in studying the structure and function of a gene and its mutations that cause various genetic disorders. The HGP, launched in 1989, was targeted at determining the complete nucleotide sequence of the human genome. Mercifully, it culminated in the sequencing of the human genome. This has greatly expanded our ability to study human genes and to explore the roles of genes in both rare and common disorders. The genome, as is being increasingly appreciated, includes far more than a coded store of information to produce proteins. The human genome has around 25,000 genes. These encode the wide variety of proteins found in the human body.

GENETICS IN HUMAN WELLBEING

Box 40.1 summarizes the important applications of genetics. **Molecular genetics** has revolutionized the whole field of medicine with fast increasing understanding of the heritable disorders and advances in approach to diagnosis, genetic counseling and screening of subjects at risk for genetic diseases. The field promises the treatment of the diseases through direct correction of a mutation at the deoxyribonucleic acid (DNA) level. In some cases it may be possible to replace a normal or modified gene for an erratic one. The so-called **gene therapy** is now in the thick of a breakthrough.

HUMAN CELL DIVISION

Development of a new human being follows fertilization of the ovum by a spermatozoa. The composition of the zygote

determines the so-called **traits of the new individual**. The somatic cell has a cytoplasm and a nucleus that consists of chromatin. Its central structure is the gene that is located on the chromosome. The principal constituent of gene is DNA which is supposed to perform the following two functions:

1. Control of various enzymes of the cell that govern the cellular metabolism
2. Replication for reproduction

Cell division occurs in two forms—mitosis and meiosis.

Mitosis is the longitudinal division of each chromosome, occurring in all somatic cells in an asexual manner. The daughter cells contain the same number of chromosomes as the parent cell. **Meiosis** is the sexual division and occurs during gametogenesis. The homologous chromosomes are arranged in pairs. By a process of dysjunction, one member of the pair passes into each cell. After division, resulting cells (haploid) have half the number of chromosomes.

As and when division occurs, each gene produces a similar copy of itself. Nevertheless, at times, the internal organs of the gene are altered during division. This is what is termed **mutation** and the new gene or the **mutant gene**. The variations in humans, a reflection of differences at the DNA level, in the form of mutations have a definite impact on the health and functioning of a gene. There are, of course, variations that do not have any impact on the health and functioning of a gene. These are called **polymorphisms**. The term, **missense mutation**, is employed when in a mutation the base is changed within an exon, leading to change of a corresponding amino acid in the protein.

THE GENES

By definition, the genes are the hereditary material that code for the **characters** and are linearly arranged on the chromosomes, each occupying specific locus. Each gene is made up of DNA in which genetic information lies. Interestingly, it is a sheer 3% of DNA in the human genome that symbolizes genes. The remaining 93% of DNA is considered junk DNA implying that it has no particular function.

Its fundamental configuration resembles a rope-ladder with ropes that are made up of alternating deoxyribose and phosphate molecules and each rung consisting of guanine, cytosine, adenine and thymidine. The whole structure is twisted into a double helix (Fig. 40.1). This sequence (triple code) forms the template of ribonucleic acid (RNA). The

Box 40.1 Important applications of genetics

- Contributes to better understanding of etiology of disease.
- Contributes to appreciation of the mechanism behind the normal variations between individuals.
- Prevention of genetic disorders through prenatal diagnosis and genetic counseling.
- Treatment of certain genetic disorders through correction or replacement of the defective gene (genetic engineering).
- Resolution of medicolegal problems involving disputed parentage through determination of blood groups or other hereditary characteristics.

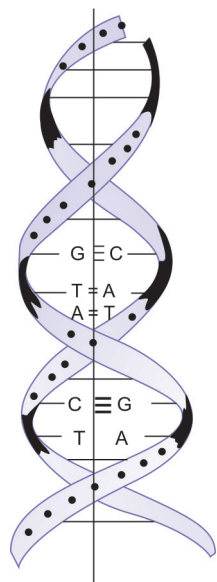


Fig. 40.1: DNA double helix.

latter transfers the message to the ribosome in protoplasm of cell from chromosomes in the nucleus and interprets in the shape of an amino acid sequence.

The genes are always paired. If a particular individual carries identical genes, he is said to be **homozygous**. If, on the other hand, he carries different genes, he is heterozygous. In determining the resulting trait, one member of pair of genes may only express. This gene is termed **dominant gene**. The gene which fails to express is called **recessive gene**. The term, **phenotype** is referred to the outward appearance of an individual. The underlying genetic constitution is called **genotype**. The term, **genome**, is used for entire HGP. Each human cell contains two copies of the genome amounting to 6 million base pairs (bp) of DNA. Phenocopy means that an environmental defect causes a clinical profile that mimics genetic defect. The term is, thus, a mimic of phenotype.

Types of Inheritance and Single Gene Disorders

- **Autosomal dominant traits:** A homozygous person produces heterozygous offspring if he mates with a normal partner. If both the partners are heterozygous, the offsprings may be 3 affected (2 heterozygous, 1 homozygous) and 1 normal. If a heterozygous mates with a normal, result may be a normal or an affected offspring in a ratio of 1:1.

Examples: Hereditary spherocytosis, achondroplasia, Huntington chorea, neurofibromatosis, tuberous sclerosis, myotonic dystrophy, osteogenesis imperfecta.

- **Autosomal recessive trait:** Here the disease will manifest only when gene is present in homozygous state. To produce the homozygous state, two carriers have got to meet, a situation which is certainly uncommon. In the parents with affected offsprings for a recessive gene, the incidence of first-cousin marriages are high as 40% compared to the very low figure of 0.4% in the random population.

Examples: Majority of the inborn errors of metabolism, including phenylketonuria (PKU), alkaptonuria, galactosemia, thalassemia, sickle-cell anemia, Morquio disease, Hurler syndrome, retinitis pigmentosa, Laurence-Moon-Biedl syndrome, Marfan syndrome, achondroplasia and cystic fibrosis.

- **Autosomal codominant inheritance:** Here, two dominant genes are said to impose upon a recessive gene.

Examples: A and B blood groups dominate over O group.

- **X-linked dominant inheritance:** Here, affected males transmit the trait to daughters only. The heterozygous affected female transmits the trait to either sex offspring's in a 1:1 ratio. In case of a union between the affected partners, 3 of the 4 offsprings are likely to be affected. X-linked dominant disorders are relatively uncommon.

Examples: Vitamin D-resistant rickets (hypophosphatemia), fragile X syndrome (FMR-I), Rett syndrome, orofaciogigital syndrome, incontinentia pigmenti, generalized hypertrichosis.

- **X-linked recessive inheritance:** Here, overt disease occurs in the male and is transmitted by a carrier female.

Examples: Hemophilia A and B, Duchenne muscular dystrophy, glucose-6 phosphate dehydrogenase (G6PD) deficiency, nephrogenic diabetes insipidus, Hunter syndrome, ocular albinism, X-linked ichthyosis, color blindness.

- **Mitochondrial inheritance:** It is also termed as **cytoplasmic inheritance**, this is purely a maternal inheritance since mitochondria are present only in mother's ovum. In other words, all offsprings are affected. Among them, girls transmit the disease and sons are affected, but do not transmit the disease.

Examples: Mitochondrial encephalopathy lactic acidosis stroke-like syndrome (MELAS).

- **Polygenic inheritance:** This means that rather than having a sharp division between the normal and the abnormal, several conditions just represent a spectrum of a continuously varying attribute.

Examples: Hirschsprung disease.

Variations in Expression of Genetic Traits

Certain hereditary traits may be suppressed or brought out by factors such as—accidental skipping of a generation and environmental influences. A person may inherit the abnormal genes. But he may only suffer from a very slight defect, not obvious to the casual observer, but otherwise detectable by radiologic studies and/or by biochemical methods. This is called **reduced expressivity of the gene**.

The term, **penetrance**, applies to the perceptual frequency with which a heterozygous dominant or a homozygous recessive gene manifests itself. When there is no detectable expression of abnormal genes, **skipping of a generation** is ascribed to **reduced penetrance**. An important instance of environmental influences is hemolytic anemia manifesting in a G6PD deficient individual. This happens only when he is exposed to such agents as are dependent for their metabolism on this very enzyme.

CONSANGUINITY

The term, **consanguinity**, denotes union between two blood relations. By **consanguineous marriage** is meant a marriage between two persons who have one or more ancestors in common. Understandably, consanguineous partners carry the same genes (normal or defective) to varying an extent depending on their closeness in terms of the family tree.

- **First degree** means between father and daughter, mother and son, brother and sister incest. In this case 50% of genetic material of parents passes on to the offspring. Mercifully, such unions seldom take place.
- **Second degree** means between uncle and niece or aunt and nephew. Grandparents and half siblings fall in this category. In this case 25% of genetic material of parents passes on to the offspring.
- **Third degree means** between first cousins. In this case 12.5% of genetic material of parents passes to the offspring. Understandably, more the genetic material passing on to the offspring, higher is the chance of transmission of parents' genetic disorder to the offspring.

TYPES OF GENETIC DISORDERS

Genetic disorders may be of 5 types:

1. Chromosomal disorders
2. Single gene disorder
3. Multifactorial (polygenic) disorders
4. Mitochondrial disorders
5. Somatic cell disorders (cancer-producing).

PEDIGREE CHART

A pedigree chart is a shortened symbolic representation of family information such as generations, number and sex of offsprings, marriage and health status. This should be considered an essential part of evaluation of a genetic disorder. Generations are represented by vertical lines. Horizontal lines represent siblings.

Symbols

The chart makes use of certain symbols (Fig. 40.2). Figures 40.3 to 40.6 depict the pedigree chart for various inheritances.

THE CHROMOSOMES

The chromosomes, rod-like basophilic structures made of closely coiled chromatin, are the **seat of the genes**. Like genes, these also exist in pairs.

Number

There are 22 pairs of identical chromosomes (autosomes) and a pair of sex chromosomes in each cell, the total being 46. The latter is labelled XY in males and XX in female. This number is termed **diploid number**. Nevertheless, in spermatozoa and ova, the number of chromosomes is only, 23, i.e. just half of the diploid number. This is termed **haploid number**. A female germ cell always has X chromosome. On the other hand, a male germ cell either has X or Y

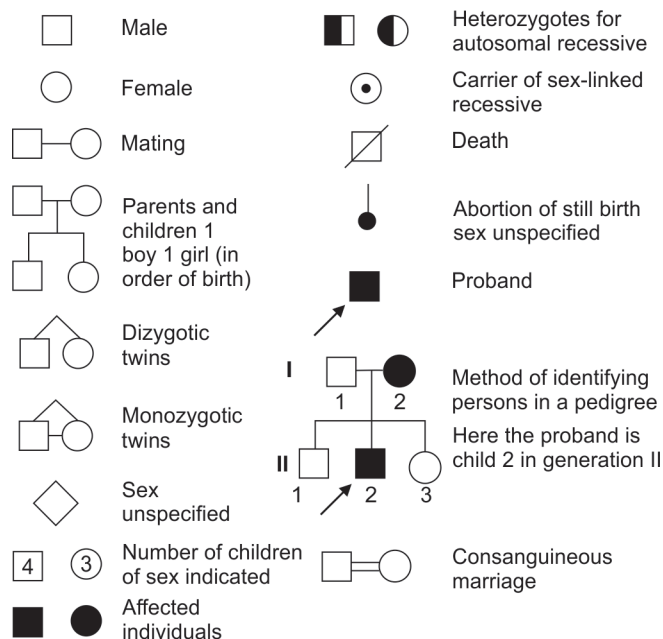


Fig. 40.2: Pedigree chart: Standard symbols employed in its construction.

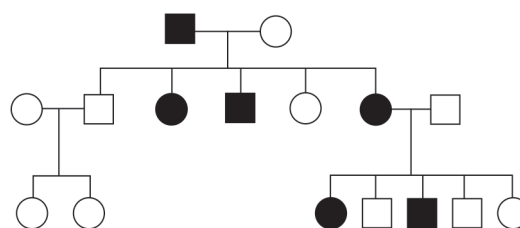


Fig. 40.3: Autosomal dominant inheritance.

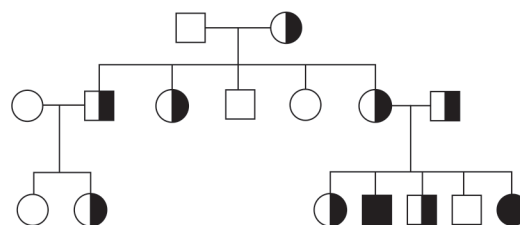


Fig. 40.4: Autosomal recessive inheritance.

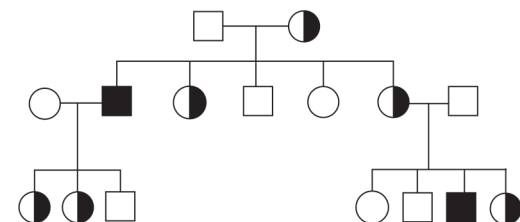


Fig. 40.5: X-linked recessive inheritance.

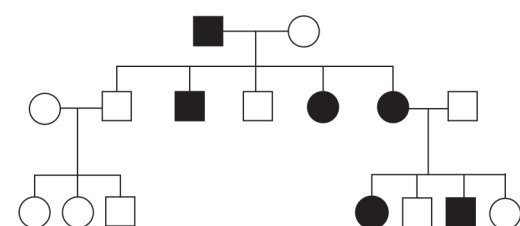


Fig. 40.6: X-linked dominant.

764 chromosome. Thus, if a female gamete (ovum) is fertilized by a sperm carrying X chromosome, the fertilized ovum will have a configuration XX and the child will be female. If a female gamete (ovum) is fertilized by a sperm carrying Y chromosome, the outcome will be XY configuration and, therefore, a male child (Figs 40.7A to G).

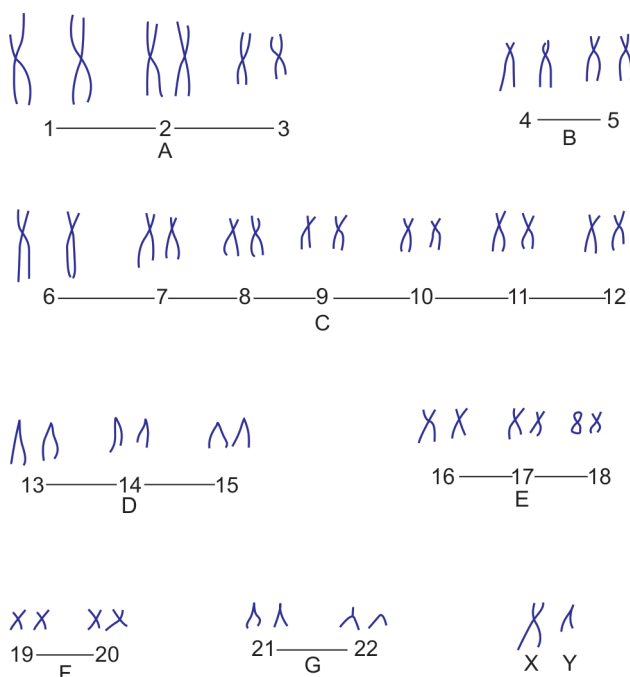
Size, Shape and Structure

Most chromosomes vary from 4–6 microns in length. In addition to the rod-like appearance, chromosomes may assume twisted, spiral or curved shape. Chemical constituents of a chromosome are DNA, RNA, histones and acidic proteins.

Each chromosome consists of two rod-shaped structures (**chromatids**) which are identical, lie parallel to each other, and are united at a constriction (primary constriction), termed **centromere**. Thus, each chromatid is divided at the centromere into two arms (Fig. 40.8).

Types

Depending on the position of the centromere in relation to the two strands called **chromatids**, each chromosome falls in one of the following types:



Figs 40.7A to G: Male karyotype. Note the XY pattern against the XX pattern in females.

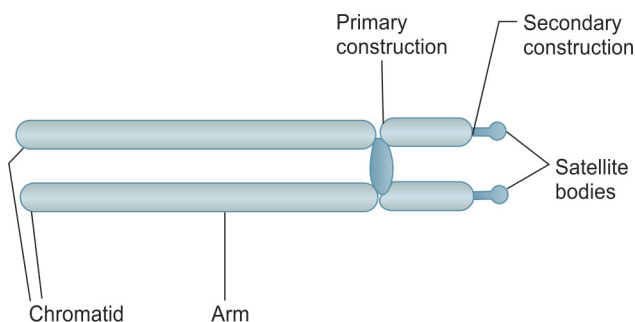


Fig. 40.8: Structure of chromosome.

Box 40.2

Modified Denver classification of chromosomes

- **Group A:** No. 1–3
- **Group B:** No. 4–5
- **Group C:** No. 6–12
- **Group D:** No. 13–15
- **Group E:** No. 16–18
- **Group F:** No. 19–20
- **Group G:** No. 21–22
- **Sex chromosomes:** XX in female, XY in male.

- **Metacentric**, when arms are equally long and centromere is central.
- **Submetacentric**, when arms are unequal and centromere is away from the center.
- **Acrocentric**, when centromere is almost at the end and a satellite is present.
- **Telocentric**, when centromere is terminal and each chromatid has one arm only.

Denver Classification (Modified)

Box 40.2 lists modified Denver classification of chromosomes.

Sex Chromatin

The characteristic of female cells is the presence of chromatin masses in the nuclei, the so-called **Barr bodies**. Skin and buccal mucosal nuclei (around 25–60%) are positive for such bodies (chromatin positive) in females. Identical bodies, called **drumstick**, are also found in 1–3% polymorphs in females.

Chromosomal Studies

Chromosomal studies are indicated in the following situations:

- Confirming diagnosis in suspected chromosomal disorders such as Down syndrome, Turner syndrome, Klinefelter syndrome, etc
- Investigations of a child with ambiguous genitalia
- Determination of sex of an unborn child
- In separation of X or Y bearing spermatozoa
- In determining effects of environmental or occupational hazards on chromosomes. Two major techniques are:
 1. Karyotyping in which complete chromosomal complement of an individual's leukocytes is studied
 2. Study of:
 - Sex chromatin or barr bodies
 - Fluorescent bodies in buccal smear
 - Drumsticks in polymorphonuclear (PMN) leukocytes.

CHROMOSOMAL DISORDERS

- **Changes in number:** The chromosome number may be an exact multiple for haploid number (23), e.g. 46, 69, 92,.... The term, **euploid**, is applied to this situation. When there is a deviation from one of the euploid numbers, the situation is called **aneuploid**. When chromosome number is just more than normal, it is termed, **polyploid**.

- In **Klinefelter syndrome (XXY)**, there is an extra X. In Turner syndrome (XO), an X chromosome is missing. Other sex chromosome aberrations include triple-X or superfemale, XYY male and XX male. Chances of mental retardation and skeletal defects are enhanced by extra X chromosome.
- In a trisomy, there is a nondisjunction of the concerned chromosome. In Trisomy 21 (Down syndrome), the two homologues fail to go to the opposite poles of the dividing cell. Trisomy 13 (D), also called **Patau syndrome** and **trisomy 18 (E)-Edward syndrome**—rank prominently among the various other trisomies described to date. These are, of course, rare. Occasionally, chromosomal division may result in cells with different number of chromosomes. This is called **mosaicism**.
- **Deletion:** There may occur deletion of the short arm of chromosome 5 (Cri du chat or cat cry syndrome), short arm of chromosome 19, or long arm of chromosome 21 or 22 (antimongolism). Deletion of the long arm of chromosome 22 with the translocation of the deleted segment on to chromosome 9 is associated with chronic myeloid leukemia.
- **Translocation:** Two types are recognized—reciprocal and centric fusion or Robertsonian translocation. The former means exchange of segments between two homologous chromosomes. The latter involves acrocentric chromosomes in which the breaks occur close to the centromeres of recipient and donor chromosomes.
- **Ring chromosome:** When both tips of chromosomes are broken and ends of centric fragment rejoin forming a chromosome with a deletion of both arms; the chromosomes are called **ring chromosomes**.
- **Inversion:** This term is applied when segment between two chromosomes breaks, a single chromosome is inverted, and order of the genes is reversed. Inversion may be pericentric or paracentric. Figures 40.9 to 40.13 highlights salient features of Down syndrome, Edward syndrome, Patau syndrome, Turner syndrome and triple X syndrome. Table 40.1 provides salient features of leading chromosomal disorders.

HIGH-RISK GENETIC DISORDERS AND CANCER

Table 40.2 lists the high-risk genetic conditions predisposing to cancer. It is obvious that number of genetic



Figs 40.9A to D: Down syndrome. (A) Note the striking facial features; (B) Scrotal tongue; (C) Sandal big toe; (D) Chromosomal pattern showing trisomy 21.

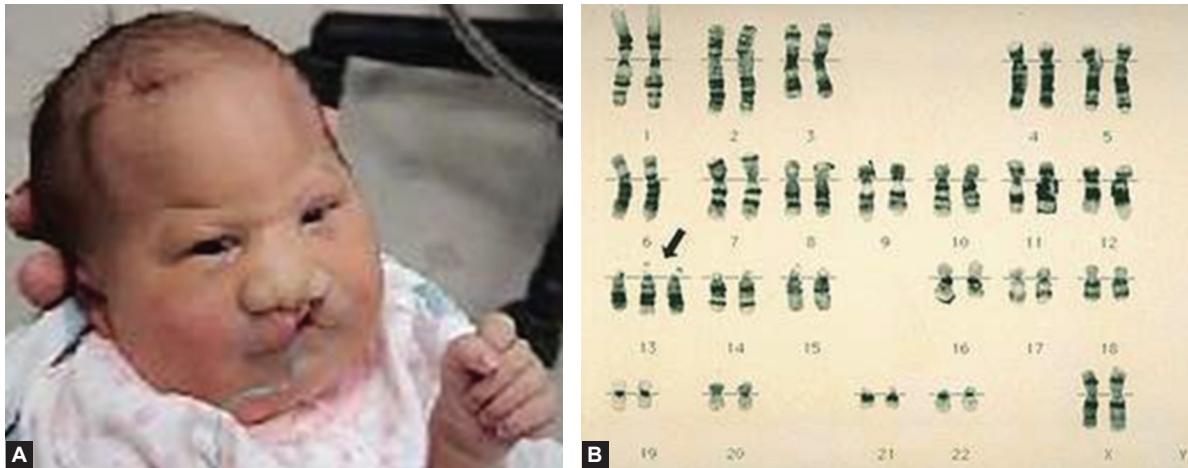


Fig. 40.10: Trisomy 13 (Patau syndrome). (A) Clinical profile; (B) Chromosomal pattern.

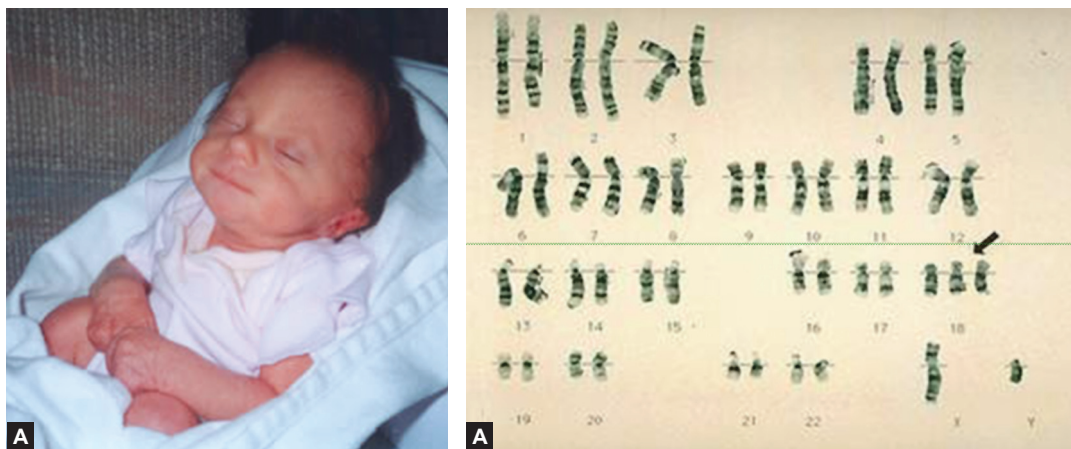
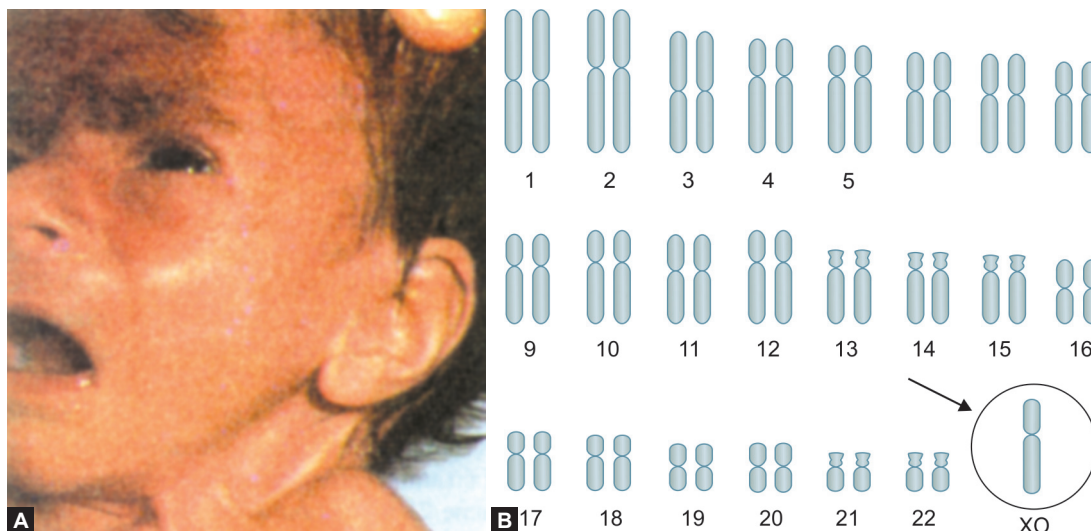


Fig. 41.11: Trisomy 18 (A) Clinical profile; (B) Chromosomal pattern.

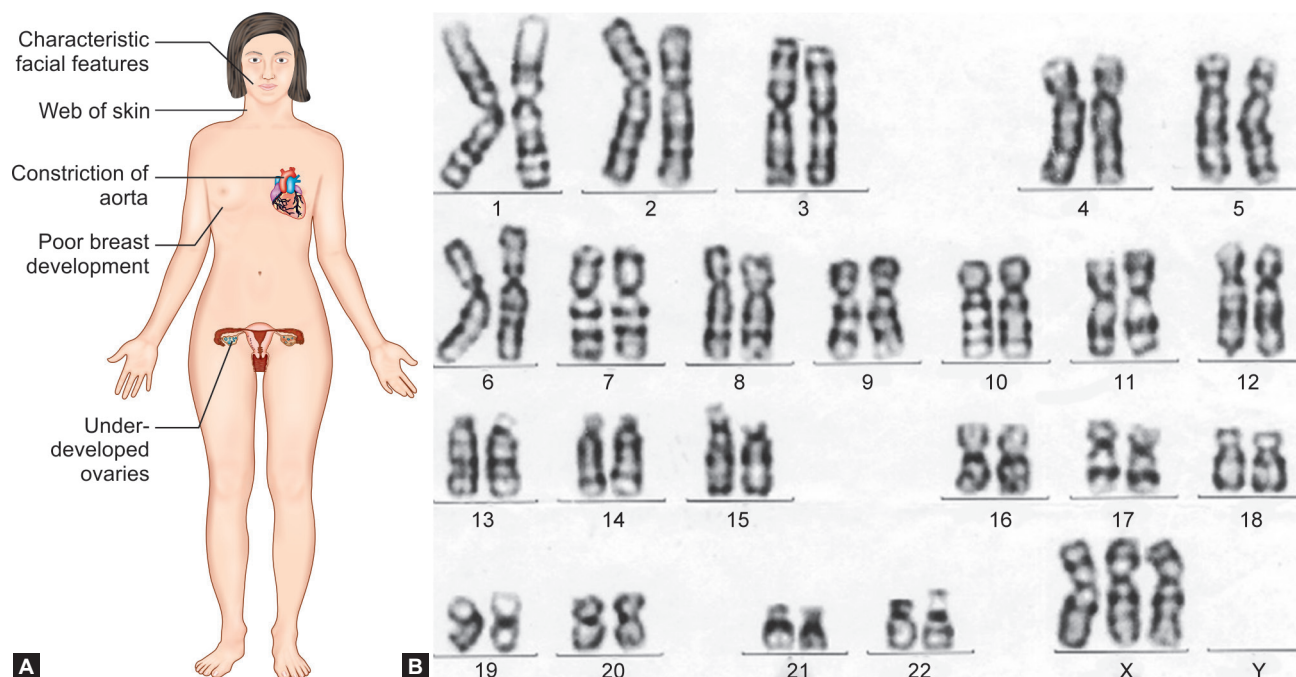


Figs 40.12A and B: Turner syndrome. (A) Classical webbing of the neck; (B) Chromosomal pattern. Note that at 23rd level, it is XO rather than the normal, i.e. XY.

conditions predisposing to cancer is by no means high. Yet, there are families in which quite a few individuals suffer from cancer the so-called *cancer families*. Genetic counseling should be of advantage to persons from such genetic families.

APPROACH TO A CHILD WITH A GENETIC DISORDER

- **Step 1:** Detailed history with special reference to consanguinity and presence of such a disorder in any



Figs 40.13A and B: Triple X syndrome. (A) Clinical profile; (B) Chromosomal pattern.

Table 40.1: Salient features of major chromosomal disorders

Syndromes	Chromosomal aberration	Incidence	Manifestations
Down syndrome	Trisomy 21, translocation mosaicism	1 in 600–800 8	Mental retardation, microcephaly with brachcephaly, Outward slant of eyes, epicanthal fold, short neck, short stature (Fig. 40.9)
Patau syndrome	Trisomy 13	1 in 20,000 births	Cleft lip, polydactyly and flexed fingers, hemangiomas, broad, flat nose, low-set malformed ears, microcephaly, microphthalmia, hypoplastic or absent ribs, genital and visceral anomalies, including cardiac and cerebral (Fig. 40.10)
Edward syndrome	Trisomy 18	1 in 8,000 births	LBW, closed fists, narrow hips with poor abduction, cardiac rocker-bottom feet, microcephaly, microphthalmia, cardiac vascular and renal anomalies, mental retardation; 95% mortality in infancy (Fig. 40.11)
Mosaicism	Trisomy 8	Not known	Long face with high forehead, broad upturned nose, thick everted lower lip, low-set ears, high-arched/cleft palate, microretrognathia, osteoarticular anomalies, moderate mental retardation
Turner syndrome	Loss (total or a part) of sex chromosome Pattern: 45, XO	1 in 8,000 livebirths	Short stature, peripheral edema, lymphadema, extra skin fold/webbing of neck renal and anomalies, gonadal dysplasia, some learning disability, absence of sex characters, infertility, treatment with estrogens (Fig. 40.12)
Klinefelter syndrome	An extra X chromosome Pattern: 47, XXY Variants with more than X chromosomes	1.3 in 1,000 livebirths; 80 in 1,000 in mentally retarded; 100–200 in 1,000 in infertile males	Relatively tall stature, gynecomastia, slow development of secondary sex characters, azoospermia, small testes, infertility, psychosocial, may accuse behavior maladjustment, mental retardation; treatment replacement therapy with testosterone (Fig. 40.13)
XXX males	Additional Y chromosome(s)	1 in 1,000 livebirths	Relatively tall stature, behavioral problems, infrequently genital anomalies, radioulnar dysostosis and prolonged PR interval
Fragile X syndrome	Fragile site at Xq 27,3 of distal long arm of chromosome X; due to change in size of DNA sequence (allelic expansion)	Most common cause of mental retardation in males	Mental retardation, long face with prominent jaw and large ears, macroorchidism

Abbreviations: DNA, deoxyribonucleic acid; LBW, low birth weight.

Table 40.2: High-risk genetic conditions predisposing to cancer

Single gene disorders	Chromosomal disorders
Neurofibromatosis	Down syndrome (trisomy 21)
Tylosis	Deletion 13q14
Polyposis	Deletion 11p13
Fanconi anemia	Sex chromosome anomaly
Albinism	Chromosome 8/14 translocation
p53 gene	Chromosome 9/22 translocation (philadelphia chromosome).

family member in the present generation as well as previous generations. Take at least three generations into account.

- **Step 2:** History of exposure to adverse environmental influences such as chemicals, radiation, etc.
- **Step 3:** Pedigree chart construction.
- **Step 4:** Detailed physical check-up, not missing out on anthropometry.
- **Step 5:** Clinical diagnosis with photographs as a reference point in future.
- **Step 6:** First line investigations; complete blood count and other hematological, biochemical and radiological tests.
- **Step 7:** Cytogenic studies as and when indicated.
- **Step 8:** Sophisticated tests such as DNA, PCR, etc., if indicated to arrive at the final diagnosis.
- **Step 9:** Therapeutics for comorbidities if no cure available for the disorder.

- **Step 10:** Genetic counseling.
- **Step 11:** Follow-up.

THERAPEUTICS IN GENETIC DISORDERS

Pending further advancements in complete cure of genetic disorders, therapeutics aimed at reducing the comorbidities such as worsening manifestations, complications, handicap, irreversible damage, etc. should be in place (Table 40.3).

GENE THERAPY

Definition

Gene therapy is defined as application of genes for altering the pathological disease process. In other words, it is the treatment of a genetic disease by introducing healthy genes into the patient's body. Close on the heels of identification of genetic alterations leading to diseases, advances are in progress to alter the pathological disease processes by employing genes. In three such diseases, success has already been attained.

Prerequisites

Box 40.3 lists the genetic disorders that may be fit for gene therapy.

Gene Therapy Trials

Following successful gene therapy in adenosine deaminase (ADA) deficiency, familial hypercholesterolemia and certain malignancies, scores of gene transfer experiments on humans are being actively pursued (Table 40.4).

Table 40.3: Therapeutics in various genetic disorders

Action	Specific therapy and genetic disorder(s)
Withholding of certain drugs	<ul style="list-style-type: none"> • Oxidising agents (e.g. quinine, sulfas, fava beans) in G6PD deficiency • Phenobarbital and other barbiturates in porphyria
Withholding of certain foods/agents	<ul style="list-style-type: none"> • Milk in galactosemia • Phenylalanine in PKU
Administration of chelating agents	Desferrioxamine in hemochromatosis, including thalassemia major, penicillamine in Wilson disease
Enzyme induction	Phenobarbital in Crigler-Najjar and neonatal hyperbilirubinemia for inducing hepatic microsomal enzymes such as glucuronyl transferase
Bypassing enzymatic block	Coenzyme B6 in homocystinuria
Replacement therapy	<ul style="list-style-type: none"> • Thyroxine in congenital hypothyroidism • Cortisone in adrenogenital syndrome, factor VIII/XI in hemophilia
Bone marrow/stem cell transplantation	<ul style="list-style-type: none"> • Primary immunodeficiencies • Thalassemia major • Hurler syndrome
Substitution of micronutrients	Vitamins in some IEMs
Transfusion	Blood or factor VIII in hemophilia
Physical and social support	<ul style="list-style-type: none"> • Physiotherapy and rehabilitation • Measures aimed at adjustment in the family and elsewhere
Avoidance of exposure	Trauma in hemophilia, sunlight in albinism, porphyria, xeroderma pigmentosa
Surgery	Corrective operative intervention in some malformations
Gene therapy	<ul style="list-style-type: none"> • Adenosine deaminase deficiency • Familial hypercholesterolemia • Certain malignancies.

Abbreviations: PKU, phenylketonuria; G6PD, glucose 6 phosphate dehydrogenase; IEM, inborn error of metabolism.

Box 40.3 Genetic disorders that may be fit for gene therapy

- Disorders for which the gene stands identified
- The function of the identified gene is precisely clear
- The disorder is monogenic recessive
- Target cells of the disorder are easily accessible
- Animal models are available.

The Technique

The process of introducing a therapeutic gene into the target cells is termed **gene transfer**. The cells containing the newly transferred gene are called **transduced with the particular gene**. Gene transfer is carried out either by transfection or infection.

Transfection means the direct delivery of DNA to cells. The transfer through infection involves a virus vector. Retroviruses are the vector of choice for most gene therapy protocols. Adenoviruses and liposomes are also being employed for this purpose. Two procedures of gene therapy are:

1. In vivo
2. Ex vivo (Fig. 40.14)

The **in vivo** therapy involves direct delivery of the gene transfer vector to the patient. The **ex vivo** therapy involves removal of target cells from the target organ, introduction of therapeutic genes into these cells and then infusion of the cells back to the patient.

Prerequisite

- A central prerequisite for gene therapy is that the disorder must be a single gene disorder of recessive inheritance.
- DNA sequence for the gene should be available for purpose of transfer.

Adverse Effects

All said and done, it must be appreciated that gene transfer may be accompanied by major adverse effects on the patient, including transfer of a potentially dangerous infection. This snag and other difficulties in the way of

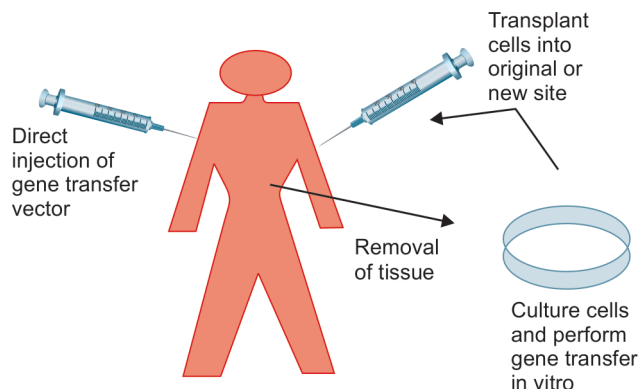


Fig. 40.14: In vivo versus ex vivo gene therapy. In vivo gene therapy involves direct delivery of the gene transfer vector to the patient. In contrast, ex vivo gene therapy involves removal of tissue from the target organ, delivery of the gene transfer vector to cultured cells, and transplantation of the modified cells back into the patient.

positive outcome of gene therapy are likely to be overcome in the near future. With further advances in successful genetic engineering, quite a few ethical, social and policy issues may also need to be ironed out.

PREVENTION OF GENETIC DISORDERS (Community Genetics)

Since, curative treatment of most genetic disorders is not available at present and there are genuine difficulties in managing them, efforts directed at their prevention need to be promoted. It can be carried out at various levels, namely:

- Prevention of occurrence of defect(s)
- Prevention of recurrence in the family
- Early diagnosis for disability limitation.

Avoidance Spectrum

Box 40.4 identifies certain actions/practices, if avoided, contribute to prevention of genetic disorders.

Molecular Detection of Carrier State (Carrier Screening)

Availability of sophisticated molecular techniques has come in handy in detecting female carriers of recessive

Table 40.4: Some of the remarkable gene therapy trials

Disorder	Gene inserted	Target cells	Current status
ADA deficiency	Adenosine deaminase	Lymphocytes	Successful
AIDS kinase	HSV thymidine	CD+T-cells	
Neuroblastoma	IL-2	Tumor cells	
Cystic fibrosis of pancreas	CFTR	Airway epithelium, pancreas	
Hemophilia A and B	Factor VIII and IX	Fibroblasts	
Beta-hemoglobinopathies	Beta globin	Blood formed elements	
Familial hypercholesterolemia	LDL receptor	Liver, smooth muscle cells, epithelium of blood vessels	Successful
PKU	Phenylalanine hydroxylase	Liver	
Gaucher disease	Acid beta-glucosidase, glucocerebrosidase	Macrophages, liver, lung, spleen	
Alpha 1-antitrypsin Deficiency	Alpha 1-antitrypsin	Lungs, liver	

Abbreviations: ADA, adenosine deaminase deficiency; AIDS, acquired immunodeficiency syndrome; PKU, phenylketonuria; CFTR, cystic fibrosis transmembrane conductance regulator; LDL, low density lipoprotein; HSV, herpes simplex virus; IL, interleukin.

Box 40.4

Identifies certain actions/practices that contribute to prevention of genetic disorders

- Avoid consanguineous marriages/unions.
- Avoid pregnancy at advanced maternal age as a safeguard against nondisjunction chromosomal disorders.
- Avoid pregnancy at advanced paternal age as a against single gene mutations of autosomal dominant.
- Avoid exposure to radiation and toxic chemicals that predispose to mutations.
- Avoid marriage between individuals from two families having same genetic disorder.
- Avoid marriage between carriers of same genetic trait, e.g. thalassemia.

disorders (both autosomal and X-linked) in conditions such as hemophilia, Duchenne muscular dystrophy (DMD), G6PD deficiency; carriers of beta thalassemia trait, etc. in high-risk families/groups/communities.

Newborn Screening

Screening of newborns for certain preventable diseases (PKU, hypothyroidism, congenital adrenal hyperplasia {CAH}, galactosemia, tyrosinemia, etc) and then providing early treatment is a normal practice in prosperous countries. It is yet to pick up in India. The topic is discussed in Chapter 17 (Neonatology).

Periconceptional Folic Acid

This strategy of administering oral folic acid a month before and 2–3 months after conception has proved of considerable value in prevention of neural tube defects. For details, See Chapter 28 (Pediatrics Neurology).

Prenatal Diagnosis

Prenatal diagnosis is mainly based on:

- Fetal ultrasonography
- Maternal serum screening—pregnancy-associated plasma protein A, free beta-human chorionic gonadotropin (HCG) in first trimester; serum alpha-fetoprotein, HCG, unconjugated estriol and inhibin A in second trimester
- Invasive prenatal testing—chorionic villous biopsy at or after 10–12 weeks of gestation; amniocentesis at 16–20 weeks; cord blood sampling after 18 weeks may help in detecting and preventing birth of infants who suffer from untreatable genetic disorders.

Genetic Counseling

Genetic counselling is the process by virtue of which the patients and/or close relatives at risk of an inherited disorder are advised about the:

- Consequences and nature of the disorder,
- Probability of developing or transmitting it,
- Options open to them in management and family planning. More details are provided at the tailend of the chapter.

GENETIC COUNSELING

Definition

The term, **genetic counseling**, denotes informing the individuals and/or families about the present and future possible genetic disorder(s) and the various options available for safeguarding from recurrence of such a disorder or minimizing its adverse effects. In other words, it is a communication process that involves occurrence or recurrence of genetic disorders in a family, coping with it and minimizing its adverse consequences.

Indications

- A genetic disease in an index case or a family member.
- Birth defects/malformations/anomalies in a previous child.
- Unexplained dysmorphism, multiple malformations, mental retardation, etc. in a child.
- Exposure to teratogenic influences (drugs, toxoplasmosis other agents, subella, cytomegalovirus and herpes simplex {TORCH} group of infections) during pregnancy.
- Ultrasonography showing malformations in the fetus.

Prerequisites

Before talking to the family in which a child is diagnosed as suffering from a genetic disorder, the pediatrician must ensure that the following prerequisites are satisfied:

- Construction of an accurate pedigree chart
- Documentation of prenatal, antenatal and delivery history
- Review of the available information about the disorder
- Detailed clinical check-up of the affected child, including the photographs and measurements
- Confirmation of the diagnosis by the relevant tests
- Preparedness with information regarding support groups for the benefit of the family
- Preparedness with the ongoing information about the disorder and new modalities for its management for conveying it to the family.

The components of the counseling session should include:

- Exact or round about diagnosis; when that is not possible, differential diagnosis
- Natural history of the disorder with prognosis and potential therapy, as also referral to a better center/institution
- Genetic aspects and recurrence risk of the disorder
- Prenatal diagnosis and prevention, e.g. ultrasonography for neural tube defects, amniocentesis/chorionic villus sampling for chromosomal abnormalities, biochemical disorders and DNA studies
- Support groups
- Follow-up in which benefits of new information about the concerned genetic disorder should be provided to the child/parents.

DERMATOGLYPHICS

This term is derived from the (*Greek words—derma meaning skin and glyphi meaning curve*).

Definition

Dermatoglyphics, therefore, refer to the study of ridge and flexion patterns in handprints, soleprints and fingerprints.

Normal Dermatoglyphic Pattern

Normally, fingerprints show three ridge patterns—(1) arch, (2) loop and (3) whorl. The ulnar loops are maximum on digit 3 and 4 though they are dominant in all the digits. In digit 1 and 4, whorl pattern is maximum. Radial pattern is dominantly seen on digit 2. Arches are far less with maximum frequency in digit 2 and 4. The point where the three ridge systems meet is best seen at the base of the fingers on the palm. These points are termed **triradii**. The triradius lying close to the wrist is called **axial triradius**.

Likewise, the three basic patterns of the palmar creases are the usual palmar crease, the single palmar crease and Sydney line. The last two are called **simian creases** (Fig. 40.15).

Deramtoglyphics in Disease

It is now established that these ridges develop between the second and the fourth months of embryogenesis. In case of abnormal embryogenesis during this period, abnormalities of dermatoglyphic patterns may result. In other words, presence of abnormal dermatoglyphic patterns reflects some developmental insult, such as chromosomal disease, during the second to fourth months of gestation.

In Down syndrome, trisomies 13 and 18 and certain X-linked disorders, characteristic dermatoglyphic patterns have been described. It is of value to measure the angle subtended between the axial triradius at the triradii at the base of the index and little fingers. It is called **atd angle**. In normal individuals it measures around 45 ($<57^\circ$), but

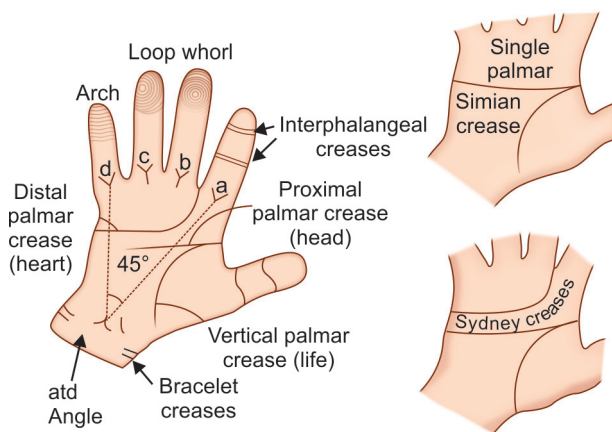


Fig. 40.15: Dermatoglyphic patterns.

it may be as much as 90° in Down syndrome and 110° in trisomies 13–15.

There is a strong association between Simian crease on one hand and Down syndrome and leukemia on the other hand. It is expected to be present in 50% of cases of Down syndrome and in high proportion of autosomal trisomies. The total ridge count in **Klinefelter syndrome** is considerably reduced as compared to the normal of 128 to 145. In female, it is zero. It seems that the count is inversely proportional to the number of sex chromosomes an individual possesses. The ridge count in Turner syndrome is as high as 178. Dermatoglyphics in acute rheumatic fever show that position of axial triradius is abnormal with ulnar deviation (tu) with or without distal displacement ($t''u$ or $T''u$) resulting in abnormal atd angle. Abnormal dermatoglyphics have also been reported in conditions such as Indian childhood cirrhosis, congenital heart disease and protein energy malnutrition.

Multiple Choice Questions

- Spot the wrong observation:
 - Genetics deals with transmission of characters from parents to offsprings
 - Only 30% of DNA in the human genome symbolizes genes, rest has no function
 - According to Denver classification of chromosomes, group D means chromosomes 16–18
 - The characteristic of female cells is the presence of chromatin masses in the nuclei, the so-called Barr bodies
- All are having X-linked recessive inheritance, except:
 - Hemophilia A and B
 - Duchenne muscular dystrophy
 - Color blindness
 - Achondroplasia
- Edematous hands or feet at birth are a feature of:
 - Down syndrome
 - Turner syndrome
 - Patau syndrome
 - Edward syndrome
- Rocker bottom feet is the feature of:
 - Down syndrome
 - Patau syndrome
 - Turner syndrome
 - Klinefelter syndrome

contd...

5. Gene therapy is currently available for all of the following, except:
 - A. Cystic fibrosis
 - B. Adenosine Deaminase (ADA) deficiency
 - C. Familial hyperchloremia
 - D. Certain malignancies
6. A 25-day-old neonate presents with bilateral cataract, seizures and vomiting. What is your diagnosis?
 - A. Galactosemia
 - B. Toxoplasmosis
 - C. Rubella
 - D. Cytomegalic virus infection

Answers

- A. B 2. D 3. B 4. B 5. A 6. A

Clinical Problem-solving

Review 1

A 10-year-old boy presents with chronic diarrhea and moderate protein energy malnutrition. He is being investigated for the cause of his chronic diarrhea. What draws the attention of the clinicians is that, additionally, he is found to be having moderate mental retardation with an IQ of 40, long face with prominent jaw, large ears and macroorchidism. Karyotyping clinches the diagnosis.

1. What is the most likely diagnosis for his moderate mental retardation, long face, prominent jaw, large ears and macroorchidism?
2. What do you expect in karyotyping in this case?
3. Is it a frequent cause of mental retardation?

Review 2

A 14-year-old boy presents for low intelligence (IQ 55) and short stature with a height of just 143 cm. Examination shows webbing of the short neck, low posterior hairline and increased carrying angle.

1. What is your clinical diagnosis?
2. What is chromosomal pattern in this condition?
3. In which way does it differ from Turner syndrome?

Answers**Review 1**

1. Fragile X syndrome.
2. Xq27.3 of distal long arm of chromosome X as a consequence of change in size of DNA sequence (allelic expansion).
3. Fragile X syndrome is the most common cause of mental retardation.

Review 2

1. Noonan syndrome.
2. Chromosomal pattern is normal 45 XY.
3. Noonan syndrome differs from Turner syndrome in two ways. First, against the classical pattern of 45 XO in Turner syndrome, there is no chromosomal abnormality in Noonan syndrome. Secondly, Noonan syndrome occurs invariably in boys whereas Turner syndrome is restricted only to females.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS /INTERNET

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GENERAL CONSIDERATIONS

Ever since Garrod described almost a century back four inherited metabolic disorders, there has been continued addition to the list. Today, hundreds of disorders, mostly rare and autosomal recessive, are recognized. Their number is no doubt on a constant increase, largely with the availability of advanced techniques for their identification as also increasing index of suspicion on the part of medical profession. According to the World Health Organization (WHO), prevalence of inborn errors of metabolism (IEM) globally is in the vicinity of 3–5%. An interesting feature of such disorders is that they usually have their clinical manifestations in almost all systems.

DEFINITION

Inborn errors of metabolism are defined as disease entities caused by genetic defects concerning synthesis, metabolism, transport or storage of biochemical compounds. As a consequence, deficiency of one or more enzymes needed for formation or transport of proteins occurs.

In recent years, advances in molecular biology have added considerably to our understanding of IEMs. An aspect of mitochondria is one such field. Mitochondria are structures within cells that convert the energy from food into a form that cells can use. Each cell contains hundreds to thousands of mitochondria, which are located in the fluid that surrounds the nucleus (the cytoplasm).

Mitochondria produce energy through oxidative phosphorylation. This process uses oxygen and simple sugars to create adenosine triphosphate (ATP), the main energy source of the cell. A set of enzyme complexes, designated as complexes (I–V), carry out oxidative phosphorylation within mitochondria.

In addition to energy production, mitochondria play a role in several other cellular activities. For example, mitochondria help regulate the self-destruction of cells (apoptosis). They are also necessary for the production of substances such as cholesterol and heme (a component of hemoglobin). Most IEMs are of autosomal recessive inheritance.

Etiopathogenesis

IEMs are the consequence of mutations in the deoxyribonucleic acid (DNA) which code for a specific protein that acts as an enzyme, receptor, transport vehicle, membrane pump or structural element. Absence of a single enzyme leading to disturbance in that particular metabolic pathway

Box 41.1 Classification of IEM with major specific conditions

Disorders involving intoxication

- Aminoacidopathies—PKU, maple syrup disease
- Organic aciduria
- Urea cycle defects
- Disorders of carbohydrate metabolism
- Disorders of copper metabolism
- Porphyrria.

Disorders of energy metabolism

- Mitochondrial disorders
- Disorders of glycolysis
- Disorders of glycogen metabolism
- Disorders of gluconeogenesis
- Hyperinsulinism.

Disorders of complex molecules

- Lysosomal storage diseases
- Peroxisomal disorders
- Alpha 2-antitrypsin deficiency
- Congenital disorders of glycosylation.

Abbreviations: IEMs, inborn error of metabolism; PKU, phenylketonuria.

(accumulation of compounds proximal to the enzymatic block or deficiency of product distal to it) is the underlying causative factor in a large majority of the cases.

Pathophysiological Classification

In terms of pathophysiology, three groups are recognized:

1. **Disorders involving intoxication:** This group includes disorders of intermediary metabolism. Here, toxic compounds accumulate in the body, causing symptoms that may be acute or chronic/progressive in nature.
2. **Disorders of energy metabolism:** Here the core problem is deficient energy production or its utilization in liver, muscles, heart and central nervous system (CNS).
3. **Disorders of complex molecules:** Here manifestations are progressive and permanent. Box 41.1 presents the specific disorders falling under each group classification.

Clinical Presentation

Acute Presentation

Early onset (even on the very first day of life), especially in preterm neonates, points to a severe disease. Delayed onset suggests an intermediate or mild disease. Usually, the term neonate appears normal at birth, but then unexpectedly shows deterioration in health status. Manifestations include vomiting, breathlessness, tachypnea, seizures, floppiness and a peculiar body/urine odor depending

Box 41.2**Systemic involvement in chronic/progressive IEMs**

- **CNS:** Developmental delay/regression of milestones, severe irritability, psychomotor retardation, seizures, ataxia, spasticity and dystonia,
- **Neuromuscular:** GSD and mitochondrial myopathy
- **Liver:** Icterus (unconjugated/conjugated), hypoglycemia, hepatomegaly
- **Heart**
- **Renal:** Enlarged kidneys in GSD type I; progressive kidney injury in cystinosis; tyrosinemia, hereditary, fructose intolerance, galactosemia,
- **Ocular:** Cataracts in Wilson disease, galactosemia, Fabry disease, Lowe syndrome, peroxisomal defects; corneal cloudiness in MPS, dislocation of lens in homocystinuria, cherry-red spots in Tay-sach disease, Niemann-Pick disease, GM1 gangliosidosis
- **Skin:** Alopecia and eczema in biotinidase deficiency; angiokeratoma in Fabry disease, fucosidosis and beta-mannosidosis.

Abbreviations: CNS, central nervous system; IEMs, inborn error of metabolism; GSD, glycogen storage disease; MPS, mucopolysaccharidoses.

on the causative IEM. In older infants and children, manifestations include vomiting, episodic altered sensorium, ataxia, abdominal pain, exercise intolerance, arrhythmias, quadriplegia and drowsiness progressing to coma. Child may just develop encephalopathy without any warning signs.

Additional features include facial dysmorphism, cataract, retinopathy, deafness, hepatomegaly, myopathy, cardiomyopathy and multicystic dysplastic kidneys, etc. A remarkable feature is that in between the episodes of just-described symptomatology, child may remain symptom free – at times over a period of a year or more. Factors precipitating the episodes of symptoms include superimposed illness, exercise, fasting, enzyme inducing agents and high protein diet.

Chronic/Progressive Presentation

In this group, onset is insidious in the form of:

- Unexplained developmental delay
- Failure to thrive
- Dysmorphic coarse facies, cataract, dislocation of lens
- Chronic dermatosis, abnormal hair
- Abnormal urine color
- Seizures
- Organomegaly
- Systemic involvement (Box 41.2).

AMINOACIDOPATHIES**PHENYLKETONURIA (PKU)**

This is a rare hereditary autosomal recessive defect due to deficiency of enzyme, phenylalanine hydroxylase (or simply phenylalanine). This enzyme is responsible for converting phenylalanine to tyrosine. At least four types are known.

Clinical Features

- The child with classic PKU is usually blonde and blue-eyed due to absence of the pigment, melanin.



Fig. 41.1: Phenylketonuria. Note the eczema and lighter color of hair and skin compared to family members. Sweat in this infant was typically musty. Left untreated, mental retardation and seizures develop invariably in this IEM.

- Though he may look normal at birth, in due course he begins to have vomiting, irritability and anorexia.
- Excessive sweating gives a peculiar musty odor.
- Eczema from action of phenylalanine and its metabolites (Fig. 41.1).
- Convulsions, mental retardation with hyperactive personality and erratic behavior may become obvious as the child grows.

Diagnosis

It is by demonstrating serum phenylalanine level exceeding 1000 $\mu\text{mol/L}$ and by ferric chloride test or Phenistix paper strips showing excess of phenylalanine and its metabolites in the urine. A neonatal screening program for PKU is now available in several countries. The methods employed are:

- Guthrie card bacterial inhibition assay (BIA)
- Fluorometric analysis
- Tandem mass spectrometry.

Once newborn screening yields positive results, confirmation is obtained by molecular genetic testing of the phenylalanine hydroxylase (PAH) gene.

Treatment

A low phenylalanine diet must begin before the baby is 2 weeks old, maintaining the serum phenylalanine at about 120–360 $\mu\text{mol/L}$ (2–6 mg/dL), if mental retardation is to be prevented. For improved outcome, tetrahydrobiopterin, 5–10 mg/kg, may be employed as an adjuvant therapy.

ALKAPTONURIA

This was the very first IEM described by Garrod way back in 1908.

Etiology

This rare autosomal recessive disorder is the result of aberrant tyrosine metabolism and accumulation of homogentisic acid in body and urine because of deficiency of homogentisic acid oxidase enzyme.

Clinical Features

Manifestations include discolored urine (dark brown-black), pigmentation of face, nose, ears and eyes (ochronosis) and degenerative arthritis.

Diagnosis

Diagnosis is from a positive Benedict's test and ferric chloride test which gives purple-black color on a urine sample.

Treatment

No specific therapy is available for this benign condition.

HOMOCYSTINURIA

Etiology

This autosomal recessive disorder results from high concentration of homocysteine and its dietary precursor (methionine) in blood and other body fluids because of deficiency of cystathionine beta-synthase enzyme.

Clinical Features

Manifestations, usually begin after infancy, include mental retardation, skeletal abnormalities such as scoliosis, pectus excavatum, arachnodactyly (Fig. 41.2), thromboembolism and ocular abnormalities (ectopia lentis, myopia, cataract, strabismus, keratitis, iris atrophy, spherophakia, uveitis, pupillary block, glaucoma, retinal detachment, optic atrophy).

Diagnosis

Diagnosis is by demonstration of high levels of methionine and homocysteine in body fluids and/or assay of the enzyme in liver biopsy. Prenatal diagnosis is available.

Treatment

This treatable IEM responds favorably to dietary restrictions of methionine plus vitamin B₆ (pyridoxine).



Fig. 41.2: Arachnodactyly. Note the unusual long fingers in a case of homocystinuria with tall stature and cataract. The closest differential is Marfan syndrome.

MAPLE SYRUP* URINE DISEASE

Etiology

Maple syrup urine disease (MSUD) results from failure of decarboxylation of branched chain amino acids (leucine, isoleucine and valine) because of deficiency of the enzyme, branched chain ketoacid dehydrogenase.

Clinical Features

Manifestations of the classical MSUD start in neonatal period and include poor feeding, seizures, hypertonicity, lethargy, refractory hypoglycemia, metabolic acidosis and coma. Body fluids, especially sweat and urine, have a characteristic odor of maple syrup. Hence, the name.

Diagnosis

Diagnosis is confirmed by demonstrating high levels of branched chain amino acids in urine and blood.

Treatment

Treatment is diet low in branched chain amino acids (say, a special synthetic formula) and thiamine. In acute exacerbation, excess of the offending amino acids needs to be removed from circulation by peritoneal dialysis with IV administration of high energy nutrition. Prognosis is guarded. Untreated neonates die within weeks.

HARTNUP DISEASE

Etiology

In this rare autosomal recessive disorder, a defective transport of tryptophan in the gut and renal tubules leads to deficiency of nicotinic acid.

Clinical Features

Manifestations simulating pellagra includes photosensitive dermatitis, psychiatric symptoms, headache, ataxia, diplopia and tremors. Factors such as sulfa drug therapy, infection, undernutrition and stress are known to precipitate the symptoms.

Diagnosis

Diagnosis is by demonstration of large amounts of indoles and indicans in urine.

Treatment

Treatment is administration of nicotinic acid, 50–300 mg/day, plus protection from exposure to sunshine.

TYROSINEMIA TYPE I

Tyrosinosis, Hereditary Tyrosinemia, Hepatorenal Tyrosinemia.

Etiology

Tyrosinemia type I, an autosomal recessive trait, results from raised serum tyrosine level because of deficiency of

* Maple syrup is the sap from the xylem of sugar maple or various other species of maple trees. It consists of primarily sucrose and water, with small amounts of the monosaccharides glucose and fructose from the invert sugar created in the boiling process.

776 fumarylacetoacetate hydrolase enzyme which is largely expressed in liver and kidneys.

Clinical Features

- The neonatal or acute form manifests in first 6 months
- The latent or chronic form manifests after first year of life
- Manifestations common to both forms include:
 - Failure to thrive and developmental delay
 - Cabbage-like odor
 - Hepatic failure
- The chronic form may additionally have renal tubular dysfunction, vitamin D resistant rickets and polyneuropathy.

Diagnosis

Diagnosis is from estimation of specific enzyme activity in liver biopsy or cultured fibroblasts. Tyrosinemia type II (oculocutaneous tyrosinemia), a rare autosomal recessive disorder, results from deficiency of enzyme, tyrosine transaminase. Manifestations include mental retardation, hyperkeratosis of palms and soles, corneal ulcers, etc. Liver and kidneys are spared.

Treatment

Treatment of tyrosinemia consists of a diet low in tyrosine, phenylalanine and methionine (only in type I). Type I may eventually need liver transplantation. Transient tyrosinemia of the newborn, resulting from delayed maturation of enzyme, p-hydroxyphenyl pyruvic acid oxidase, is usually a self-limiting condition occurring predominantly in preterm neonates on high protein formula. Manifestations in symptomatic cases include feeding difficulty, lethargy and poor motor activity. Reduction in intake of protein plus vitamin C helps to correct the aberrant state.

UREA CYCLE DEFECTS

The common denominators of the six defects in enzymes involved in urea cycle are hyperammonemia along with amino acid metabolism.

Clinical Features

- Partial enzyme deficiency may cause only mild symptoms which may occur after months or years of birth.
- Manifestations, as and when these become evident as episodes (often following a “stress”) include poor appetite, nausea, vomiting, lethargy and behavior problems.
- Intolerance to/disliking of protein foodstuffs.
- Classical form manifests in newborns with feeding difficulty, irritability, vomiting, lethargy, hypothermia, tachypnea, seizures and progressive drowsiness culminating in coma.

Diagnosis

In a clinically suspected child, the following investigations are needed:

- To establish urea cycle defect:
 - Plasma ammonia more than 80 µg/dL

- Blood glucose-normal
- Anion gap-normal
- To establish specific defect:
 - Plasma amino acid analysis
 - Urinary orotic acid
- For definitive diagnosis:
 - DNA analysis
 - Enzyme activity analysis.

Treatment

- Mainstay of treatment is:
 - Rapid elimination of ammonia and a check on its production by restriction of protein
 - Correction of dehydration and dyselectrolytemia
 - Attention to intercurrent infection(s).
- Pharmacotherapy includes:
 - Sodium benzoate
 - Essential amino acids
 - Arginine.

ORGANIC ACIDURIAS (OAs)

These are a group of conditions characterized by excretion of nonamino-organic acids in urine on account of enzyme deficiencies in pathways of amino acid degradation.

Clinical Features

In infants, it manifests a few days after birth in the form of a toxic encephalopathy with vomiting, feeding difficulty, seizures, lethargy and drowsiness progressing to coma. In older children and adolescents, presentation may be in the form of Reye-like syndrome, recurrent ketoacidosis, neurological disease with ataxia and seizures or psychiatric manifestations such as intellectual dysfunction. Table 41.1 lists the specific manifestations in certain OAs.

Diagnosis

- Urine analysis for organic acids by gas chromatography with mass spectrometry
- Serum acylcarnitine profile by tandem mass spectrophotometry
- Urinary organic acid profile
- Diagnosis is confirmed by:
 - Measuring the activity of deficient enzymes in lymphocytes or cultured fibroblasts
 - DNA analysis.

Treatment

- **Thiamine responsive MSUD:** Adjunctive therapy with cofactor or thiamine
- **Methylmalonic academia:** Hydroxocobalamin
- **Propionate metabolism disorders:** Metronidazole, intermittently for 1–2 weeks.

Prognosis

Early diagnosis and timely treatment improve the outcome.

Table 41.1: Specific manifestations in certain organic acidurias

Manifestation	OAs
Abnormal odor	<ul style="list-style-type: none"> Burnt sugar—MSUD Sweaty feet—isovaleric acidemia, glutamic aciduria type 2 Cat urine—multiple carboxylase deficiency
Skin problems	Perioral eruption—multiple carboxylase deficiency
Hair abnormalities	Alopecia/sparse hair—biotinidase deficiency
Dysmorphism	Mevalonic aciduria, glutaric aciduria type 2, 3(OH)isobutyric aciduria
Hypoglycemia with CNS symptoms	Organic acidurias, late onset MSUD
Acute ataxia	Late onset MSUD, methylmalonic acidemia, isovaleric acidemia, multiple carboxylase deficiency,
Acute metabolic encephalopathies	Isovaleric acidemias, MSUD, glutaryl-CoA dehydrogenase deficiency and propionic acidemia, methylmalonic acidemia, multiple carboxylase deficiency,
Acute hemiplegia and metabolic stroke	Propionic acidemia, methylmalonic acidemia, glutaric acidemia type 1, methylcrotonyl-CoA carboxylase deficiency.

Abbreviations: CNS, central nervous system; OA, organic aciduria; MSUD, maple syrup urine disease.

CARBOHYDRATE METABOLISM DEFECTS

GALACTOSEMIA

This again is a rare autosomal recessive defect, due to absence of the enzyme galactose-1-phosphate uridylyl-transferase, which is responsible for converting galactose to glucose. With the missing of the said enzyme, galactose accumulates in the blood and tissues. Besides this classical form, two additional forms of galactosemia are—galactokinase deficiency and uridyl diphosphogalactose-4 epimerase deficiency.

Clinical Features

- The child starts manifesting the disease as soon as milk—the main source of galactose—is given to him.
- He has feeding difficulties, vomits and fails to thrive.
- Jaundice and hypoglycemic convulsions may occur in the neonatal period.
- Hepatomegaly starts quite early though development of splenomegaly may take some time.
- Pseudotumor cerebri occurs in some cases.
- If the treatment is delayed and the patient survives, cataracts* (Fig. 41.3) and gross mental retardation follow in due course of time.
- Damage to the kidneys may cause albuminuria and aminoaciduria.



Fig. 41.3: Cataract. Galactosemia is an important cause of early-onset cataract.

Diagnosis

Investigations demonstrate galactosemia, hypoglycemia and galactosuria. Erythrocytes show increased level of galactose-1-phosphate.

Treatment

It consists of absolute withdrawal of milk and its products from the diet. After several years, the child may be able to tolerate galactose-containing foods. To prevent mental retardation and cataract, progesterone has been found to be of value.

GLYCOGEN STORAGE DISEASE

At least a dozen types of glycogen storage disease (GSD) are known (Box 41.3), each resulting from deficiency of one or the other enzyme in the synthesis or breakdown of glycogen. All are rare and usually acquired as autosomal recessive conditions.

GLYCOGEN STORAGE DISEASE TYPE IA (Von Gierke Disease)

It is the most common GSD and is due to deficiency of glucose-6-phosphatase enzyme.

Box 41.3 Important types of glycogen storage disease

- GSD type 0, due to deficiency of enzyme, glycogen synthase, is characterized by severe hypoglycemic seizures in infancy
- GSD type 1a (Von Gierke disease)
- GSD type 1b
- GSD type 1la (Pompe disease) is characterized by progressive cardiomegaly and heart failure
- GSD type 1lb is characterized by muscular dystrophy without involvement of the heart.
- GSD type III or Crohn's disease is characterized by involvement of liver, striated muscles and red cells.

Clinical features mimic those seen in Type 1.

- GSD IIIa (Cori/Forbes)
- GSD IV (Anderson)
- GSD VI (Hers)
- GSD V (McArdle disease)
- GSD IX
- Remaining GSDs are of sheer academic interest.

Abbreviation: GSD, glycogen storage disorder.

* Other causes of early-onset cataract include Hurler syndrome, Lowe syndrome, gangliosidosis and low birth weight.



Fig. 41.4: Glycogen storage disease. Note the massive hepatosplenomegaly and doll face appearance.

Clinical Features

- Doll like face
- Stunted growth
- Hepatomegaly (usually massive) (Fig. 41.4)
- Ketonuria, hyperuricemia, bleeding tendency and hypoglycemic convulsions.

Diagnosis

It is confirmed by liver biopsy which shows increased fat and glycogen and absence of glucose-6-phosphatase.

Complication

Gout may complicate the clinical picture after puberty.

Treatment

- It is frequent feeding during day time and night time glucose IV infusion or continuous nasogastric feeding to ensure normoglycemia.
- Soda bicarbonate may be given to prevent acidosis.
- Some subjects may require allopurinol for safeguarding against hyperuricemia and uric acid nephropathy.
- In persistently high triglyceride levels (<900 mg/dL), nicotinic acid and fibrates may be given.

LYSOSOME STORAGE DISEASES

GAUCHER DISEASE

It is a kind of lipidosis and is inherited as an autosomal recessive condition.

Etiology

The cause is deficiency of the enzyme, beta-glucosidase, in brain, liver, spleen, bone marrow and other organs.

Clinical Features

The *infantile type* is characterized by rapidly progressive visceral enlargement and mental retardation. The *juvenile*

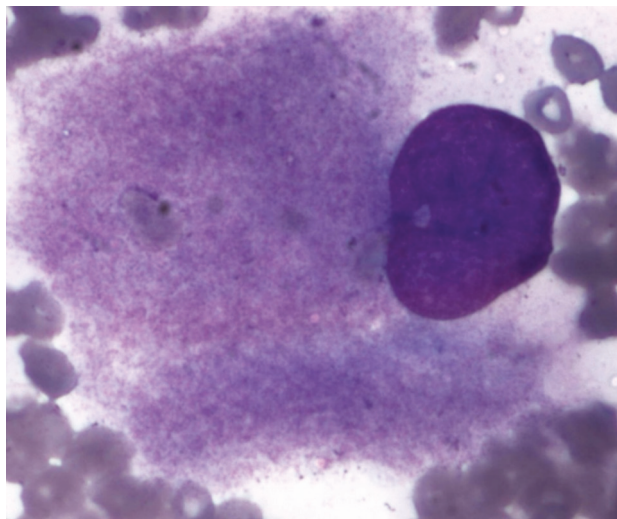


Fig. 41.5: Gaucher cell. Note the foamy, glucocerebroside-stuffed macrophage.

type is rapid in development of hepatosplenomegaly. Brain, however, remains unaffected. The *adult type*, on the contrary, is slow in progression. It is characterized by anemia, thrombocytopenia and involvement of the long bones.

Diagnosis

Diagnosis of Gaucher disease is by demonstration of typical cells, Gaucher cells, in the bone marrow or splenic puncture (Fig. 41.5).

Treatment

Treatment is symptomatic. Infantile form has the worst prognosis and progressive neurologic involvement. Death is more or less a rule.

NIEMANN-PICK DISEASE

This is another rare disease.

Etiology

A lipidosis inherited as an autosomal recessive character, in which an enzyme, sphingomyelinase, is absent. This results in accumulation of sphingomyelin in various tissues and organs (Fig. 41.6).

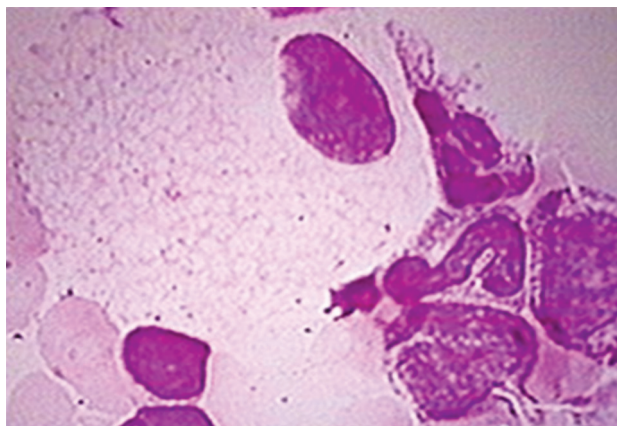


Fig. 41.6: Niemann-Pick cells. Note the foamy or soap-suds appearance.

Box 41.4 Characteristics of MPS as a group

- In each of the disorders, a special enzyme deficiency is known to occur.
- Skeletal deformities (dysostosis multiplex) are universal for MPS.
- Involvement of the CNS with progressive mental retardation is common.
- Multiple organs/systems including CVS, liver, spleen, skin, joints and tendons may be affected.
- All have autosomal, recessive mode of inheritance, the only exception being Hunter syndrome which follows an X-linked recessive trait.
- Each type is suspected clinically and the diagnosis is confirmed by demonstration of increased urinary excretion of the specific mucopolysaccharide products and the specific enzyme deficiency (Table 41.2).
- No definite treatment is as yet available for most of these disorders. The value of steroids remains doubtful.

Abbreviations: MPS, mucopolysaccharidosis; CNS, central nervous system; CVS, cardiovascular system.

Clinical Features

- The disease is characterized by mental retardation, hepatosplenomegaly, lymphadenopathy, weight loss and abdominal distention.
- A cherry-red spot may be seen in every third patient of this disease, in the region of macula.
- Anemia, usually moderate, is invariably present.
- Death generally occurs in infancy.

Diagnosis

Diagnosis is by demonstration of Niemann-Pick cells in blood, marrow or splenic puncture. Miliary tuberculosis-like picture may be seen in the X-ray of the chest.

Treatment

No effective treatment is available.

MUCOPOLYSACCHARIDOSES (MPS)

The term, MPS, refers to a group of hereditary and progressive conditions accompanied by storage of acid MPS in the tissues. MPS are caused by mutations of genes coding for lysosomal enzymes needed to degrade glycosaminoglycan's acid MPS. Box 41.4 lists the characteristic of the mucopolysaccharidoses as a group. Table 40.2 shows salient features of various MPS.

THE CHILD WITH IEM: A PRACTICAL APPROACH

A large majority of IEM manifest soon after birth while others present later with unexplained manifestations. A point of considerable importance is that invariably neonates with IEM appear normal at birth. This is ascribed to the positive support from the placenta that tends to eliminate adverse intermediary metabolites during the course of fetal life. Thereafter, an IEM may present on the very first day or later in the neonatal period per se, in infancy, childhood, adolescence and even adulthood.

WARNING SIGNS

A high index of clinical suspicion is the gateway to diagnosis. Box 41.5 list of ever increasing number of IEM

according to the type of metabolism affected. Many of these defects are dealt with elsewhere in this volume. Some of the genetic disorders of special clinical importance in pediatrics are tackled briefly and yet comprehensively in this very chapter. Table 41.3 shows inborn errors of amino acid metabolism associated with peculiar odor.

ACUTE ONSET IEM GROUP**Investigative Work-up**

- Complete blood picture
- Blood levels of glucose, electrolytes, bicarbonate, calcium, transaminases, ammonia, lactate and pyruvate, etc.
- Chest X-ray
- Neurological imaging—computed tomography (CT), magnetic resonance imaging (MRI)
- Electroencephalography (EEG)
- Echocardiography
- Ultrasound abdomen
- Cerebrospinal fluid (CSF)
- High performance liquid chromatography (HPLC) for analysis of quantitative urinary and plasma amino acids
- Tandem mass spectrometry for plasma carnitine and acylcarnitine
- Gas chromatography and mass spectrometry (GCMS) for urinary organic acids
- Specific enzyme assays
- Plasma levels of ammonia, lactate, amino acids and very long chain fatty acids, etc.
- Biochemical autopsy—it is crucial for confirmation of diagnosis.

Treatment

Empirical treatment is a rule rather than an exception. Broadly, its main features are:

- Elimination of potentially toxic compounds, e.g., protein, fat, galactose and fructose, etc.
- Adequate energy through 0.2% saline in 10% dextrose IV or intralipids infusion
- Hemodialysis for enhancing excretion of toxic metabolites
- Measures to reduce plasma ammonia levels
 - IV phenylacetate and sodium benzoate with l-arginine
 - Dialysis, preferably hemodialysis
- Carnitine in life-threatening situations
- Pyridoxine for intractable seizures
- Enzyme replacement therapy.

Finally, it is mandatory to avoid any precipitating stress such as infection, fever, fasting, surgery and trauma, etc.

CHRONIC/PROGRESSIVE IEM GROUP

The hallmark of chronic IEM is insidious onset from neonatal period to adulthood. Two types are known: grey matter disorders and white matter disorders.

Investigative Work-up

- Complete blood picture
- Liver function tests

Table 41.2: Salient features of various mucopolysaccharidoses

MPS Type	Eponym	Inheritance	Gene chromosome	Main clinical features	Defective enzyme
I-H	Pfaundler-Hurler	AR	IDUA 4p16.3	Severe Hurler phenotype, mental deficiency, corneal clouding, death usually before age 14 year (Figs 41.7A to C)	α -L-iduronidase
I-S	Scheie	AR	IDUA 4p16.4	Stiff joints, corneal clouding, aortic valve disease, normal intelligence, survive to adulthood	α -L-iduronidase
I-HS	Hurler-Scheie	AR	IDUA 4p16.4	Phenotype intermediate between I-H and I-S	α -L-iduronidase
II	Hunter	XLR	IDS Xq27.3-28	Severe course similar to I-H but clear corneae. Mild course: less pronounced features, later manifestation, survival to adulthood with mild or without mental deficiency	Iduronate sulphate sulfatase
III-A	Sanfilippo A	AR	SGSH 17 q25.3	Behavioral problems, sleeping disorder, aggression	Heparan-S-sulfamidase
II-IB	Sanfilippo B	AR	NAGLU 17q21	Progressive dementia, mild dysmorphism, coarse hair	N-Acetyl-a-D-glucosaminidase
III-C	Sanfilippo C	AR	HGSNAT 8p11.21	Clear corneas; survival to adulthood possible	Acetyl-CoA:a-glucosaminide N-acetyltransferase
III-D	Sanfilippo D	AR	GNS 12q14		N-Acetylglucosamine-6-sulfatase
IV-A	Morquio A	AR	GALNS 16q24.3	Short-trunk dwarfism, fine corneal opacities, characteristic bone dysplasia; final height below 125 cm (Figs 41.8A to C)	N-Acetyl-galactosamine-6-sulfatase
IV-B	Morquio B	AR	GLB1 3p21.33	Same as IV-A, but milder; adult height over 120 cm	β -Galactosidase
VI	Maroteaux-lamy	AR	ARSB 5q11-q13	Hurler phenotype with marked corneal clouding but normal intelligence; mild, moderate and severe expression in different families	N-Acetyl-galactosamine-4-sulfatase (arylsulfatase B)
VII	Sly	AR	GUSB 7q21.11	Varying from fetal hydrops to mild dysmorphism; dense inclusions in granulocytes	β -Glucuronidase
IX	Hyaluronidase deficiency	AR	HYALI 3p21.3	Periarticular masses, no Hurler phenotype H	Hyaluronidase 1

Source: Spranger JW. Mucopolysaccharidoses. In: Kliegman RM, Staford BF, St Geme II JW, Schor NF, Behrman WE (eds): Nelson Textbook of Pediatrics, 20th edn. Philadelphia: Elsevier 2016:737–743.

Abbreviations: AR, autosomal recessive; MPS, mucopolysaccharidoses.

- Kidney function tests
- Serum electrolytes
- Neurological imaging
- Electrophysiological studies
- Skeletal survey
- Specific enzyme assays
- Plasma levels of lactate ammonia, very long chain fatty acids and amino acids.

Treatment

A multidisciplinary team approach, including a metabolic specialist, is needed. Broadly the therapeutics include:

- Cofactor therapy
- Megavitamin therapy
- Specific diets
- Enzyme replacement therapy
- Organ transplant.

All said and done, IEMs present difficulties at all stages from presentation, suspicion, evaluation and treatment. A systematized approach, however helps to resolve most of the cases as far as possible in the existing state of knowledge, investigative services and therapeutics. Understandably, a patient with IEM in a prosperous setting is at an advantage compared to the one in a resource-limited country.

Box 41.5**Red flag signs of IEM: Situations in which IEM should be suspected****Newborns**

- Unexplained lethargy, vomiting, icterus, feeding problem, seizures, coma, tachypnea
- Odd body odor
- Hypoglycemia, acidosis, hyperammonemia, high blood or urine levels of metabolites (say amino acid or ammonia)
- Consanguinity
- Family history indicating unexplained deaths of neonates.

Infants and children

- Unexplained mental and/or developmental delay, motor deficit or seizure
- Unexplained hepatomegaly as such or with splenomegaly
 - Unexplained odd odor, especially during an acute illness: PKU-musty; maple syrup urine disease-maple syrup-like; sweaty feet-like-isovaleric acidemia; and glutaric acidemia type II; cat urine-like-3-methyl crotonyl CoA carboxylase and multiple carboxylase deficiency
 - Corneal opacity, cataract or dislocation of lens
 - Unexplained kidney stone
 - Unexplained episodic vomiting, acidosis and coma.
- Consanguinity
- Family history of progressive neurological illness-hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome*.

Abbreviations: PKU, phenylketonuria; IEM, inborn error of metabolisms.

* HELLP syndrome is characterized by 3 features, namely hemolysis, elevated liver enzyme levels and low platelet levels. It is a life-threatening condition.

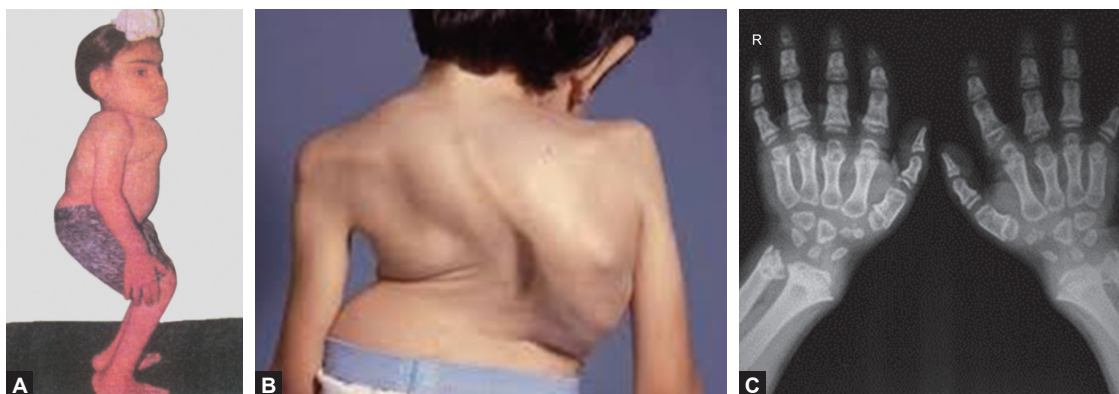
Table 41.3: Urine odor as a clue to inborn error of metabolism

IEM	Peculiarity in urine odor
PKU	Mousey or musty
MSUD	Maple syrup
Tyrosinemia	Boiled cabbage, rancid butter
Glutaric acidemia (type II)	Sweaty feet, acrid
Hawkinsinuria	Swimming pool
3-Hydroxy-3-methylglutaric aciduria	Cat urine
Isovaleric acidemia	Sweaty feet, acrid
Hypermethioninemia	Boiled cabbage
Multiple carboxylase deficiency	Tomcat urine
Oasthouse urine disease	Hops-like
Trimethylaminuria	Rotting fish

Abbreviations: IEM, inborn error of metabolism; PKU, phenylketonuria; MSUD, maple syrup urine disease.



Figs 41.7A to C: Hurler syndrome (MPS type 1). (A) Grotesque facies with large protruding tongue and corneal cloudiness, mental retardation; (B) Hepatosplenomegaly and bony deformities; (C) Involvement of sella turcica (J-shaped) in skull X-ray.



Figs 41.8A to C: Morquio syndrome (MPS type IV). (A) Note widespread skeletal deformities (short neck, short trunk, spinal curvature, barrel-shaped chest, knock knees) and characteristic facies with prominent maxillae, short nose and broad mouth (widely spaced teeth are not apparent here). The subject had hepatosplenomegaly but was mentally normal; (B) Severe scoliosis; (C) Proximally pointed and tapering (bullet-like) metatarsals, short ulna and V sign between distal ends of ulna and radius in X-ray of hands and wrist.

Multiple Choice Questions

- Spot the wrong entry:
 - Most IEMs have autosomal recessive inheritance
 - Mitochondria are necessary for the production of substances such as cholesterol and heme (a component of hemoglobin)
 - Lysosomal diseases are related to carbohydrate metabolism
 - Abrupt development of an encephalopathy without any warning sign suggests an IEM
- All of the following observations about phenylketonuria are correct, except:
 - Child is always blond and blue-eyed because of lack of pigment
 - Serum phenylalanine level exceeding 1000 $\mu\text{mol/L}$ is diagnostic
 - Tandem mass spectrometry is a part of the neonatal screening program available in western countries
 - Tetrahydrobiopterin, 5–10 mg/kg, may be employed as an adjuvant therapy
- The combination of mental retardation, skeletal abnormalities, thromboembolism and ocular abnormalities is suggestive of:
 - Homocystinuria
 - Alkaptonuria
 - Mucopolysaccharidosis
 - Fabry disease
- The combination of jaundice, feeding difficulties with vomiting, hypoglycemic convulsions and poor weight gain in a newborn is suggestive of:
 - Glycogen storage disease
 - Galactosemia
 - Gaucher disease
 - Niemman-pick disease
- The combination of short stature with dysmorphic facies, severe abnormalities of spine, hepatosplenomegaly and bullet-shaped metacarpals with nearly normal IQ is suggestive of:
 - Hurler syndrome
 - Sanfilippo syndrome
 - Morquio syndrome
 - Achondroplasia

Answers

1. C 2. A 3. A 4. B 5. C

Clinical Problem-solving

Review 1

A 10-month-old child presents hypoglycemic convulsions which are controlled following correction of hypoglycemia. Additionally, he is found to have characteristic doll-like face, growth retardation (weight 6.5 kg, length 66 cm), delayed milestones and massive hepatosplenomegaly (liver span 10 cm, spleen size grade 4).

- What is the most likely diagnosis?
- What is cause of this disease?
- How will you confirm your diagnosis?
- What is its long term complication?

Review 2

A 1-year-old mentally retarded child, product of a consanguineous union (second degree) with gnotoseque appearance, corneal cloudiness, short stature with kyphosis, umbilical hernia developmental delay and hepatosplenomegaly is referred to a tertiary care center with a provisional diagnosis of congenital hypothyroidism. Thyroid profile turns out to be normal. Imaging of skull reveals J-shaped sella turcica and dorsal and lumbar vertebrae bodies showing beak-shaped projections anteriorly.

- Your diagnosis?
- What is the enzyme defect?
- Any available treatment?

contd...

Answers**Review 1**

1. The clinical profile fits very well in the diagnosis of glycogen storage disease type 1 (von Gierke disease).
2. Enzyme, glucose 1,6-phosphatase deficiency.
3. The gold standard for diagnosis is liver biopsy which shows increased fat, glycogen and absence of the enzyme glucose 1,6-phosphatase.
4. Hyperuricemia causing gout.

Review 2

1. MPS 1H (Hurler syndrome).
2. alpha-L-iduronidase enzyme defect.
3. Stem cell therapy.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

1. Mohammed Kunju MA. Approach to neurodegenerative disorders. In: Gupte S, Gupte SB, Gupte M (eds): *Recent Advances in Pediatrics-23 Hot Topics*. New Delhi: Jaypee 2015:141–161.
2. Rozvani I, Rozvani GA. An approach to inborn errors of metabolism. In: Kliegman RM, Stanton BF, St Geme II JW, Schor NF, Behrman WE (eds): *Nelson Textbook of Pediatrics*, 20th edn. Philadelphia: Elsevier 2016:634–635.
3. Saudubray JM, van den Berghe G, Walter JH. *Inborn Metabolic Diseases: Diagnosis and Treatment*, 5th edn. New York: Springer Medizin 2011.
4. Spranger JW. Mucopolysaccharidoses. In: Kliegman RM, Staforf BF, St Geme II JW, Schor NF, (eds): *Nelson Textbook of Pediatrics*, 20th edn. Philadelphia: Elsevier 2016:737–743.

BOOK/MONOGRAPH

1. Clarke JTR. *A Clinical Guide to Inherited Metabolic Diseases of Children*, 3rd edn. New York: Cambridge University Press 2006.

DEFINITION

The term, **neuromuscular disorders**, includes the diseases of the motor unit which has four components:

1. Motor neuron in the brainstem or anterior horn of the spinal cord
2. Peripheral nerve
3. Neuromuscular junction
4. Muscle fibers innervated by a single motor neuron.

Though motor unit is under upper motor neuron control, upper motor neuron (suprasegmental) disorders such as cerebral palsy are not included under neuromuscular disorders. Presence of upper motor neuron (UPN) lesion is suggested by weakness accompanied by hypertonia, hyperreflexia, extensor plantar reflexes, seizures and poor cognition.

MOTOR NEURON DISORDERS (Anterior Horn Cell Disorders)

These include spinal muscular atrophy (SMA), poliomyelitis, polio-like illness caused by viruses such as coxsackie and echovirus, juvenile form of amyotrophic lateral sclerosis, Pena-Shokeir syndrome and Marden-Walker syndrome.

SPINAL MUSCULAR ATROPHIES

Spinal muscular atrophy is a degenerative disorder of motor neurons beginning in fetal life and continuing in infancy and childhood. It is the second most common neuromuscular disorder after Duchenne muscular dystrophy (DMD).

Classification

- SMA type 1 or Werdnig-Hoffmann disease which is a severe form.
- SMA type 2 which is a late infantile and slowly progressive form.
- SMA type 3 or Kugelberg-Welander disease which is a more chronic or juvenile form.

Etiopathogenesis

The diseases are inherited as autosomal recessive, the defective gene being on chromosome 5 at 5q 11-13 locus. The basic pathologic defect is a remarkable loss of anterior horn cells, usually from the entire length of the spinal cord.

Clinical Features

The common features are:

- Positive family history
- Absence or reduction of fetal movements in utero



Figs 42.1A and B: Spinal muscular atrophy type I (Werdnig-Hoffmann disease) (A) Hypotonia and muscular weakness: lack of resistance to passive motion and severe delay in motor development, inability to hold the head steady; (B) Facial involvement (fish mouth) and thoracic deformity.

- Gross hypotonia and areflexia in an otherwise normal child, generally at or soon after birth
- Muscle involvement is symmetrical though proximal parts are more affected. Spontaneous movements, atrophy and fasciculation of tongue may occur. In most instances of SMA type I:
- The disease progresses rapidly, proving fatal, in many cases during infancy itself
- The cause of death is neurological involvement of muscles of thorax, respiratory failure and/or fulminant infection
- The survivors are in a completely helpless condition and susceptible to infections. Figs 42.1A and B show clinical spectrum of SMA type.

Diagnosis

Muscle biopsy shows the classical features of denervation atrophy with large patches of small, atrophic fibers residual muscle fibers of normal or somewhat enlarged diameter. Sural nerve biopsy may show sensory neuropathic changes.

Treatment

Treatment is symptomatic. Nothing seems to change the course and prognosis of the disease.

PERIPHERAL NEUROPATHIES

General Characteristics

These are listed in Box 42.1.

Box 42.1 General characteristic of peripheral neuropathies

- Majority of the peripheral neuropathies are chronic.
- Most peripheral neuropathies are primarily axonal.
- Majority of the polyneuropathies exhibit distal-to-proximal gradient of manifestations.
- Involvement of proximal nerves is infrequent.
- Large fiber neuropathies cause sensory deficit, weakness and loss of deep tendon reflexes.
- Small fiber neuropathies cause distal sensory deficit, painful burning dysesthesias and autonomic dysfunction.
- Pure sensory neuropathies are extremely rare.



Fig. 42.2: Guillain-Barré syndrome. Note the acute symmetrical ascending paralysis in this infant with Guillain-Barré syndrome.

GUILLAIN-BARRÉ SYNDROME (Acute Polyradiculoneuropathy)

Guillain-Barré syndrome (GBS) is an acute polyradiculopathy that is symmetrical, ascending, rapidly progressive and predominantly motor (Fig. 42.2). The syndrome follows a preceding infection say upper respiratory tract infection (URTI) or acute gastroenteritis (AGE) within around 6 weeks and is considered an immunomediated disorder. Bulbar and respiratory involvement is frequent. For details, See Chapter 28 (Pediatric Neurology).

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

This infrequently encountered polyradiculoneuropathy has 4 forms:

1. Symmetrical
2. Asymmetrical
3. Distal predominant
4. Sensory predominant.

The symmetrical form, which is most commonly seen, is symmetrical and proximal with distal weakness in upper and lower limbs and concomitant sensory loss. Unlike GBS which takes less than 4 weeks to evolve, it takes at least 8 weeks to evolve. **Diagnosis** is by electrophysiology and nerve biopsy. **Treatment** revolves around intravenous immunoglobulin (IVIG), plasma exchange and steroids. Long-term immunomodulatory therapy is the mainstay in most cases.

HEREDITARY NEUROPATHIES

Though a large number of hereditary neuropathies exist, **Charcot-Marie-Tooth disease** is the most common as such. It is also the most common peripheral neuropathy in children. Charcot-Marie-Tooth disease is characterized by presence of distal weakness as well as wasting, distal sensory impairment, skeletal deformities and inheritance pattern. Diagnosis is by electrophysiological characteristics, inheritance pattern and nerve biopsy.

HEREDITARY MOTOR-SENSORY NEUROPATHIES (HMSN)

This is a group of progressive disorders of peripheral nerves. The group includes peroneal muscular atrophy (HMSN type I), peroneal muscular atrophy axonal type (HMSN type II), Dejerine-Sottas disease (HMSN type III), Roussy-Levy syndrome, Refsum disease, giant axonal neuropathy, congenital hypomyelinating neuropathy and leukodystrophies.

ACUTE FLACCID PARALYSIS (AFP)

In pursuit of eradicating poliomyelitis, the term, **acute flaccid paralysis**, was brought to limelight. Originally four conditions—(1) polio, (2) GBS, (3) transverse myelitis, (4) traumatic neuritis were kept under this umbrella. Later, to ensure that no case of polio was missed, all conditions with flaccidity (except central nervous system (CNS) infections, say encephalitis or meningitis) were included. AFP is detailed in Chapter 18 (Viral Infections).

BELL'S PALSY

This is an acute unilateral, lower motor neuron (peripheral) type of seventh cranial nerve paralysis (Fig. 42.3). It is not associated with other cranial neuropathies or brainstem dysfunction. Age is no bar.

Usually, Bell's palsy develops abruptly about 2 week after a systemic viral infection say herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, Lyme disease, mumps virus,



Fig. 42.3: Bell's Palsy. Note the inability to close right eye with slight deviation of mouth to opposite side.

786 *Toxocara, Rickettsia, Mycoplasma*, or human immunodeficiency virus (HIV) infection many cases are of idiopathic etiology.

An one week course of low dose prednisolone, started within few days (3–5 days) of onset followed by one week taper is helpful. Addition of oral acyclovir to the prednisolone course may be of added advantage. Usually, it resolves within a few to several months without any sequelae. Also, See Chapter 28 (Pediatric Neurology).

NEUROMUSCULAR JUNCTION DISORDERS (Neuromuscular Transmission Disorders)

Generally speaking, these are pure motor disorders in which involvement of eye muscles is a common denominator.

Myasthenia Gravis

This condition, occurring secondary to an autoimmune reaction against acetylcholine receptors, is uncommon in pediatric practice. Three types are recognized:

1. Transient neonatal myasthenia gravis
2. Persistent neonatal myasthenia gravis
3. Juvenile myasthenia gravis.

Transient Neonatal Myasthenia (Transitory Neonatal Myasthenia)

The baby acquires it from the mother with established mild or even unrecognized disease. He is floppy and weak with poor feeding, feeble cry, feeble respiratory effort, lots of oral secretions and ptosis. However, he is alert and has normal deep tendon reflexes.

Response to edrophonium/neostigmine intramuscular (IM) is excellent. Without treatment, most babies show spontaneous recovery in 2–4 weeks, but death may occur within hours or days.

Persistent Neonatal Myasthenia Gravis

There is no evidence of the disease in the mother. The symptoms are those encountered in the transient type plus severe involvement of the eyelids and extraocular muscles. Risk to siblings is high. It is likely to persist throughout life.

Juvenile Myasthenia Gravis

This occurs usually after 10 years of age with remarkably high incidence among girls, the girls: boys ratio being 6:1. The weakness is aggravated on repetitive movements and regresses on rest. Following or during stress such as an infection or surgery, life threatening myasthenia crisis may occur. In very severe form, generalized muscle paralysis may occur. Diagnosis is confirmed by edrophonium/neostigmine test and, if possible, by electric testing of neuromuscular transmission. With treatment employing anticholinesterase agents such as pyridostigmine bromide, neostigmine or ambenonium, 25% of the patients have complete cure and most patients can lead almost normal life.

CONGENITAL MYOPATHIES (Developmental Myopathies)

The term, *congenital myopathies*, refers to an heterogeneous group of congenital neuromuscular disorders such as

Box 42.2 Common features of congenital myopathies

- Hypotonia (floppiness)
- Muscle weakness that is static (nonprogressive)
- Normal or decrease tendon reflexes
- Comorbidities in the form of feeding difficulties, respiratory insufficiency, contractures and skeletal deformities.

myotubular myopathy, congenital muscle fiber type disproportion (CMFTD), nemaline rod myopathy, central core disease, benign congenital hypotonia, amyoplasia, muscular dysgenesis and arthrogryposis.

All are secondary to genetic defects. Muscle biopsy shows distinctive histochemical or ultrastructural changes. A large majority of these congenital myopathies present as floppy infant syndrome. Features common to all congenital myopathies are listed in Box 42.2.

Though clinically the various congenital myopathies may be indistinguishable from each other, each has distinct changes in muscle biopsy. These distinctive changes are detectable by immunochemical techniques and/or electron microscopy.

MYOTUBULAR MYOPATHY (Centronuclear Myopathy)

In this X-linked recessive disorder, genetic linkage is localized to the Xq28 site which is different from the Xp21 gene of Duchenne and Becker myopathies. There is a maturational arrest of fetal muscle during the myotubular stage of development at 8–15 week of gestation. Manifestations include decreased fetal movements, reduced muscle mass with gross hypotonia and poor respiratory efforts warranting ventilatory support, poor sucking and deglutition warranting gavage feeding, high-arched palate, ophthalmoplegia, thin tongue, absent or weak tendon reflexes. Muscle biopsy is diagnostic at birth. Prognosis is poor. Only 25% of the neonates with this disorder manage to survive. They are left with major physical handicaps including severe hypotonia.

BENIGN CONGENITAL HYPOTONIA

This condition, which may be familial in certain cases, is characterized by extreme hypotonia without delay in motor development.

Clinical Features

The infant's muscles are soft and flabby and remarkable range of movements is possible. Unlike Werdnig-Hoffmann disease, the fetal movement is normal. Spontaneous movements are more prominent and respiratory involvement is unusual. Tendon stretch reflexes are hypoactive or normal and there are no cranial nerve abnormalities. IQ is by and large within normal range.

Diagnosis

Diagnosis is by exclusion of other causes of floppiness (hypotonia). Muscle biopsy and brain imaging (with special reference to cerebellum) are normal.

Complications

Complications include recurrent dislocation of shoulder and other joints and spine-related problems such as compression, stretch injury or compromise of nerve roots.

Prognosis

Prognosis is generally good. No specific treatment is indicated. Most of the subjects recover fully by 8–10 years of age. Others have a stationary and nonprogressive course. Joints are always hypermobile.

MUSCULAR DYSTROPHIES

(Muscle Dystrophies)

The Greek term, **dystrophy** (*dys* meaning aberrant and *trophy* meaning nourishment) implies aberrant growth or nutrition of muscle fibers. Muscular dystrophies are a heterogeneous group of unrelated inherited disorders having different genetic trait and different clinical course and expression. Muscular dystrophies have four obligatory criteria that distinguish them from other neuromuscular disorders, namely:

1. They are primary myopathies
2. They have genetic basis
3. They have progressive downhill course
4. They have degeneration and death of muscle fibers at some stage.

DUCHENNE MUSCULAR DYSTROPHY

This, the most common form of progressive muscular dystrophies, is transmitted in an X-linked recessive manner (affecting only males and carried by females), manifests before the fifth year of life and generally proves fatal in the second decade.

Etiopathogenesis

Four hypotheses have been suggested (Box 42.3). Pathologic changes include various stages of necrosis of muscle fibers, phagocytosis of degenerating fibers, abnormally small fibers and increase in fat and endomysial connective tissue. There are signs of regeneration which eventually disappear.

Notwithstanding the X-linked recessive inheritance, some 30% subjects with DMD are new mutations without the mother being a carrier. Occasionally, DMD in its mild form may be encountered in girls. It appears that in these girls, the normal X chromosome becomes inactivated, but that with gene deletion becomes active (Lyon hypothesis). In girls with Turner syndrome (45 X₀), full blown DMD may occur when the X chromosome has the Xp21 gene deletion.

Box 42.3 Hypotheses about DMD pathogenesis

- Muscle lesions are secondary to microinfarcts as a result of disordered circulation.
- Muscle lesions are due to neuronal dysfunction.
- Genetic defect in muscle surface membranes.
- Defective DNA repair mechanism as a result of insult from some DNA-damaging agent, e.g. ionizing radiation or similar injury.

Abbreviations: DMD, Duchenne muscular dystrophy; DNA, deoxy ribonucleic acid.

Clinical Features

The earliest manifestations include difficulty in standing or walking, climbing stairs, arising from the floor or other activities involving the muscles of the pelvis. If picked up by the axillae, the boy may manifest hypotonia as early as two years. Early hypertrophy of calf muscles is also a useful sign. A waddling gait (Trendelenburg gait) may be noticed. The patient may find it difficult to comb his hair or raise his hands above the head.

A classical case shows a characteristic manner of arising from the bed to an upright position as is demonstrated in Figs 42.4A to C. This succession of movements is aptly described as “climbing up one’s own thighs” (Gowers’ sign). Lordosis and forwardly-thrust tummy are outstanding when the child stands upright. Pseudohypertrophy, especially of the calf muscles is striking (Fig. 42.5). Tendon reflexes are sluggish or absent; ankle reflex is an exception. Cardiac enlargement, persistent tachycardia and cardiac failure occur in nearly all cases some time during the disease. About 20–30% cases have mental deficiency. Intellectual impairment is a constant feature of the disease.

Diagnosis

The clinical impression may be supported by the following investigations:

- **Creatine kinase:** Remarkably high.
- **Electromyography (EMG):** Reduced amplitude and duration of motor unit potentials.
- **Muscle biopsy:** Changes described under pathology.
- **Electrocardiography (ECG):** Tall right precordial R waves; deep Q waves in limb or left precordial leads. In differential diagnosis, entities such as late Werdnig-Hoffmann disease, endocrinal myopathy, cerebral palsy, glycogen storage disease and polymyositis should be considered.

With the new developments in molecular genetics of DMD, molecular diagnosis is likely to take over creatine kinase (CK) and muscle biopsy in detecting carrier state.

Treatment

No safe and effective treatment is as yet available. Chronic steroid therapy gives gratifying initial results with improvement in muscle strength. But, it is frequently accompanied by adverse drug reactions (ADRs).

Steroid decrease the rate of apoptosis or programmed cell death of myotubes during ontogenesis and can decelerate the myofiber necrosis in muscular dystrophy. Strength usually improves initially, but the long-term complications of chronic steroid therapy become a road block. Improved long-term prognosis in muscle and myocardial outcome, as well as short-term improvement in muscle strength and steroids can help keep patients ambulatory for more years than expected without steroid treatment. Recommended agents are prednisolone and deflazacort.

Prednisolone 0.75 mg/kg/day for the 1st 10 days of each month to avoid chronic complications or deflazacort, 0.9 mg/kg/day, may be more effective than prednisolone.



Figs 42.4A to C: Duchenne muscular dystrophy. Note the classical Gowers' sign, i.e. succession of movements involved in arising from bed to an upright position. The child appears to be climbing up his own thighs.



Fig. 42.5: Duchenne muscular dystrophy. Note the bulky calf muscles.

Intravenous (IV) or subcutaneous (SC) injection of antisense oligonucleotide drugs that induce exon skipping during mRNA splicing in patients with susceptible mutations (~15% of patients) to restore the open reading frame in the DMD gene is another potential therapy.

Molecular genetic engineering is expected to provide cure for DMD through one of the following three approaches:

1. Myoblast transfer (transplant) therapy
2. Introduction of a recombinant dystrophin gene ligated to an appropriate promotor by IM injection
3. Use of retroviruses with viral DNA incorporating the deleted nucleotide sequences of the dystrophin gene.

Prognosis

Virtually all subjects become bedridden by 12 years of age. About 75% die before the age of 20 years, usually from cardiomyopathy or pulmonary complications.

Prevention

Detection of female carriers by serum CK estimation or quantitative EMG and genetic counseling based on localization of the gene using DNA polymorphism are important.



Fig. 42.6: Becker muscular dystrophy. Unlike DMD, in this myopathy the patient has fair chance of entering into third or even fourth decade of life.

BECKER MUSCULAR DYSTROPHY

Becker muscular dystrophy, a progressive myopathy wherein the suffer may live for quite a few decades, results from X-linked recessive mutation of DMD gene of Xp21. This type of pseudohypertrophy muscular dystrophy differs from DMD in the following ways:

- Onset of weakness is later.
- A relatively slower, protracted course.
- Affected boys remain ambulatory for 16 years of age or beyond against just 12 years in DMD.
- Death occurs in 20s or 30s, some living up to or beyond 40 years of age (Fig. 42.6).

SCAPULOPERONEAL OR SCAPULOHUMERAL MUSCULAR DYSTROPHY

(Emery-Diffuses Muscular Dystrophy)

This entity too has X-linked recessive inheritance. Like Becker muscular dystrophy, it has slow progression so that many subjects survive to late adult life. However, contractures at elbow and ankles develop from middle childhood and

muscles become wasted in a scapulohumeroperoneal distribution. Hypertrophy of calves does not occur and facial muscles are spared. Cardiomyopathy is more severe. Serum CPK is only slightly elevated.

MYOTONIC MUSCULAR DYSTROPHY (Myotonia Dystrophica, Steinert's Disease)

This multisystem disorder is inherited as an autosomal dominant trait. It is characterized by dysfunction in multiple organ systems, including immunological deficiencies, cataracts, endocrinopathies, dysmorphic facies, intellectual impairment and other neurological abnormalities.

Etiology

It is caused by an abnormal expansion of more than >80 of {CTG}_n repeats in the DMPK gene located on chromosome 19.

Clinical Features

- Characteristic facies are present in infancy with wasting or weakness, inverted V-shaped upper lip, thin cheeks and loss of muscle mass in the temporal fossae (Fig. 42.7).
- Also present are hypotonia, narrow head and high-arched palate.
- Myotonia, meaning a very slow relaxation of muscles after contraction, becomes evident usually after 5 years of age.
- In a severe neonatal form of the disease, occurring in offspring's of mothers with myotonic dystrophy, manifestations include club foot, contractures of multiple joints, generalized hypotonia and muscle weakness.
- Respiratory muscle weakness or apnea together with abdominal distention may necessitate gavage feeding or ventilator support.

Differential Diagnosis

It is from other rarer conditions with myotonia. Myotonic chondrodystrophy (Schwartz-Jampel disease), generalized

muscular hypertrophy, giving the child appearance of a body-builder, though the large muscles are in fact weak is outstanding. Paramyotonia is characterized by myotonia that is aggravated by exposure to cold.

Treatment

Drugs employed include:

- **Sodium channel blockers:** Phenytoin, quinine, procainamide, disopyramide, mexiletine
- **Tricyclic antidepressants:** Imipramine, clomipramine
- **Diuretics:** Acetazolamide, thiazides
 - **Beta agonists:** Albuterol
 - **Antiepileptic drugs:** Carbamazepine, diazepam
 - **Antihypertensive:** Nifedipine
 - **Steroids:** Prednisolone.

LIMB-GIRDLE MUSCULAR DYSTROPHY

This usually autosomal recessive (occasionally autosomal dominant) disorder is characterized by late onset of manifestations (middle or late childhood), involvement of muscles of hip and shoulder girdles and, later, distal muscles. Hypertrophy of calves and contractures of ankles occur in some patients. There is usually no cardiac involvement and IQ is normal.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (Landouzy-Dejerine Disease)

It has autosomal dominant inheritance and is characterized by late onset (around puberty) and slow progression. Manifestations include facial and shoulder girdle weakness followed by weakness of the muscles of the hips and anterior tibial and peroneal muscles. Thus, rounded and puckered mouth, inability to close the eyes fully in sleep, inability to whistle or hold air in the buccal cavity, scapular winging, foot drop and positive Gowers' sign and Trendelenburg gait are outstanding signs. Hypertrophy of calves is not present.

CONGENITAL MUSCULAR DYSTROPHY

The term, **congenital muscular dystrophy**, includes a group of dystrophies with autosomal recessive inheritance, onset right at birth, and a benign course. Arthrogryposis is present in all. Muscles of trunk and limbs are thin. Facial muscles are minimally affected. Tendon reflexes are poorly elicited or absent. In the most common form, **Fukuyama type**, encountered in children of Japanese, Dutch, German, Scandinavian and Turkish ethnic background, additional features are cardiomyopathy, mental retardation, seizures, microcephaly and growth failure. Muscle biopsy is diagnostic as early as in neonatal period.

ENDOCRINE MYOPATHIES

STEROID-INDUCED MYOPATHY

Myopathy in Cushing disease (natural) and Cushing syndrome (iatrogenic; usually exogenous fluorinated

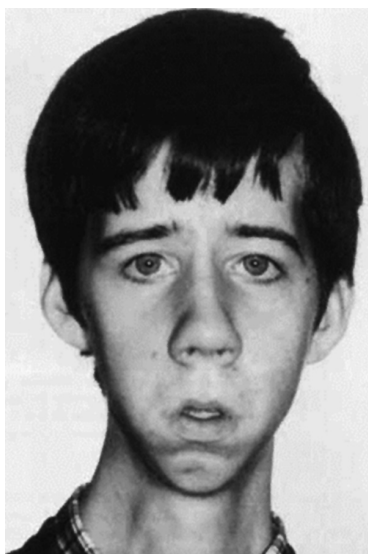


Fig. 42.7: Myotonic muscular dystrophy. Note the dysmorphic expressionless facies with inverted V-shaped upper lip. Triangular face and swan-like neck are the outcome of atrophy of mastication, facial and sternomastoid muscles.

790 steroids such as dexamethasone, betamethasone) is characterized by proximal weakness, high serum CPK, a myopathic EMG and a myopathic muscle biopsy.

Children requiring long-term steroid therapy for nephritic syndrome, asthma, juvenile idiopathic arthritis, dermatomyositis, systemic lupus erythematosus (SLE), leukemias, other autoimmune or inflammatory diseases, etc. are at considerable risk.

Vitamin D deficiency may get accentuated during chronic steroid therapy and contribute to steroid myopathy, especially in the presence of type 2 diabetes and insulin resistance. Myopathy in Conn syndrome (hyperaldosteronism), is characterized by reversible periodic weakness, high serum CPK and even myoglobinuria during an acute episode.

THYROID MYOPATHY

Hyperthyroidism (Thyrotoxicosis)

It causes myopathy in three different ways, namely:

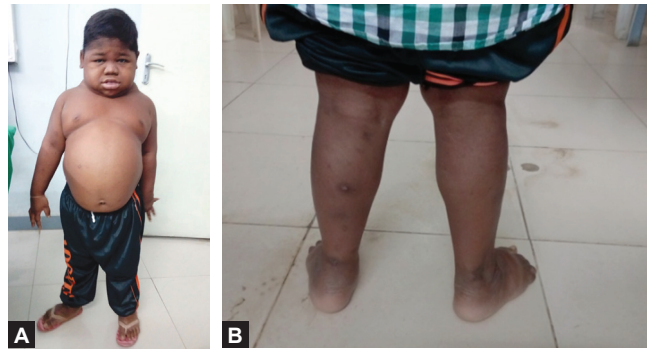
1. Binding excess thyroxine to myofibrils and impairing the contractile function (contractility)
2. Inducing myasthenia gravis
3. Inducing hypokalemic periodic paralysis, especially in East Asian males with a genetic predisposition. The thyrotoxic periodic paralysis responds to supplements of potassium and beta-blocker, propranolol. Proximal weakness and wasting accompanied by myopathic electromyographical changes are seen in thyrotoxicosis induced myopathy (Fig. 42.8).

Hypothyroidism

In hypothyroidism, proximal muscle weakness and hypotonia are invariably encountered regardless whether hypothyroidism is congenital or acquired. In Kocher-Debre-Semelaigne (KDS) syndrome, generalized pseudohypertrophy of weak muscles,



Fig. 42.8: Thyrotoxicosis. Note the exophthalmos which is believed to be the consequence of myopathy secondary to thyrotoxicosis. Besides, she had significant weakness and wasting of skeletal muscles.



Figs 42.9A and B: Kocher-Debre-Semelaigne (KDS) syndrome: Note pseudohypertrophied and bulky calves in a 12-year-old child with acquired hypothyroidism.

especially calf muscles, is an additional feature, giving the infant a “herculean appearance like in myotonia congenital (Fig. 42.9).

Serum CK level is elevated. Clinical, biochemical and pathologic features of hyperthyroid myopathy and hypothyroid myopathy resolves after appropriate treatment.

PARATHYROID MYOPATHY

In primary hyperparathyroidism, reversible fatigability, weakness, fasciculations and muscle wasting are important features. Serum and muscle biopsy remain normal. Electromyography may show nonspecific myopathic features. A small proportion of subjects develop myotonia. This needs to be differentiated from myotonic dystrophy.

METABOLIC MYOPATHIES

Metabolic myopathies are defined as a group of “myopathies secondary to failed energy production as a result of abnormalities of glycogen, lipid, or mitochondrial metabolism”. This group includes:

- Potassium-related periodic paralysis
- Malignant hyperthermia glycogenosis
- Mitochondrial myopathies
- Lipid myopathies
- Vitamin E deficiency myopathy.

Potassium-related periodic paralysis hypokalemia and less frequently, hyperkalemia cause episodic weakness or paralysis. The condition has an autosomal dominant inheritance. Manifestations include inability of the patient to move after awakening for a few minutes to hours. In children, the period in between episodes is symptom free. But, as the child grows to adulthood, frequency of episodes increases. Eventually the patient remains symptomatic permanently. Only during acute episodes:

- Serum potassium level shows alteration,
- ECG shows the T wave changes,
- CK is slight elevation
- Muscle biopsy a vacuolar myopathy.

INFLAMMATORY MYOPATHIES

Myopathy may accompany inflammatory conditions like dermatomyositis, polymyositis, focal myositis, inclusion body myositis, trichinosis, SLE, etc. Immune system



Fig. 42.10: Dermatomyositis. Note the myopathy with concurrent rash. At times, myopathy follows the rash.

seemingly causes insult to the muscles. The most common pediatric inflammatory myopathy is **dermatomyositis**.

In dermatomyositis, a small vessel vasculitis, muscle weakness is symmetrical and proximal (Fig. 42.10). Involvement of neck flexors with dysphagia is frequent. Diagnosis is confirmed by raised serum CPK, electromyography, MRI and muscle biopsy.

Therapy includes steroids, methotrexate or azathioprine as first line and IVIG, cyclophosphamide, cyclosporine, mycophenolate mofetil, rituximab or anti-TNF-alpha agents. Also, *See* Chapter 36 (Pediatric Dermatology). Trichinosis, infestation with *Trichinella spiralis*, causes inflammatory myopathy.

TOXIC/DRUG-INDUCED MYOPATHIES

Over and above steroids, many more drugs may cause a toxic myopathy. These include excessive growth hormone, cholesterol-lowering agents (statins), alcohol, chloroquine, vincristine, labetalol, colchicines, heroin, cocaine, zidovudine and D-penicillamine, etc.

AUTONOMIC NEUROPATHIES

This group includes familial dysautonomia, Hirschsprung disease, reflex sympathetic dystrophy and congenital insensitivity to pain and anhidrosis.

Familial dysautonomia (Riley-Day syndrome) is characterized by absence of tears, poor perception of painful stimuli, excessive drooling, sweating, skin blotching, and paroxysmal hypertension. Hirschsprung disease (congenital megacolon) results from absence of parasympathetic ganglion cells in both Meissner's and Auerbach's plexuses at rectosigmoid segment with or without involvement of some additional parts of distal large bowel. For details, *See* Chapter 46 (Pediatric Surgery).

Box 42.4 Causes of floppy baby syndrome

- **Benign:** Congenital hypotonia
- **Chromosomal disorders:** Down syndrome, trisomies 13–15
- **Neurological disorders:** Atonic cerebral palsy, poliomyelitis, glycogen storage disease, cerebral lipidosis, congenital myopathy, myasthenia gravis, polyneuritis polymyositis (dermatomyositis), Werdnig-Hoffmann disease, Prader-Willi syndrome
- **Endocrinopathy:** Congenital hypothyroidism
- **Nutritional:** Advanced PEM, rickets, scurvy
- **Miscellaneous disorders:** Acrodynia, Ehlers-Danlos syndrome, infant botulism, kernicterus.

Abbreviation: PEM, protein energy metabolism.

FLOPPY INFANT SYNDROME (Floppy Baby Syndrome)

Definition

The term refers to a large group of conditions associated with excessive hypotonia.

Etiology

Box 42.4 lists the causes of floppy baby syndrome. The term must be reserved for infants suffering from severe hypotonia involving all the skeletal muscles.

Clinical Features

- The floppy infant often assumes a frog-legged posture.
- He offers little resistance to passive movements of the extremities.
- There is increased range of movements at the joints.
- The assumption of the so-called **rag-doll** position on ventral suspension is characteristic (Fig. 42.11).
- An attempt to pull him up from supine position to sitting position is accompanied by head lag.

All floppy infants must be evaluated for mental retardation and seizures, especially if the cause of floppiness appears to be CNS related.



Fig. 42.11: Floppy baby. Note the characteristic “rag-doll” position on ventral suspension.

792 Comorbidities

- Feeding problems
- Intellectual disability
- Epilepsy.

NEUROMUSCULAR DISORDER: A PRACTICAL APPROACH

Invariably, the child suffering from a neuromuscular disorder is brought to the pediatrician for weakness. A systematized approach is needed to evaluate weakness for its probable cause.

Evaluation

Clinical Evaluation

Clinical work-up usually leads to a provisional diagnosis of the neuromuscular disorder. Examination of the neuromuscular system should never miss out on muscle bulk, tone and strength as also on reflexes. Box 42.5 lists some of the clues to diagnosis.

A sound **rule of the thumb** is—myopathies follow a proximal distribution of weakness and muscle wasting (except myotonic muscular dystrophy) whereas neuropathies are generally distal in distribution (except juvenile SMA). Consideration to involvement of face, tongue, palate and extraocular muscles is helpful in the differential diagnosis. **Tendon reflexes** are diminished in myopathies. In neuropathies and motor neuron diseases, these are lost. Fasciculation's of muscle, especially in the tongue, point to denervation. **Sensory abnormalities** are a sign of neuropathy. **Fatigable weakness** suggests neuromuscular pathology.

Investigative Evaluation

Important investigations include:

- Serum enzymes like CK

Box 42.5

Clinical clues to diagnosis in neuromuscular disorders

- **Weakness, hypotonia, hyporeflexia, flexor plantar reflexes:** LMN involvement
- **Wasting, fasciculation, hyporeflexia:** Anterior horn cell involvement SMA
- **Predominantly distal muscle weakness:** Peripheral, distal wasting, hyporeflexia and sensory involvement, peripheral nerve involvement (hereditary neuropathies— both sensory and motor)
- **Fatigability and fluctuating weakness:** Neuromuscular junction involvement, myasthenia gravis
- **Proximal weakness, bulk relatively preserved, reflexes relatively preserved:** Predominantly muscle disease (muscular dystrophies)
- **X-linked recessive inheritance:** Duchenne muscular dystrophy, Becker muscular dystrophy
- **Autosomal dominant:** Facioscapulohumeral dystrophy
- **Autosomal recessive:** Sarcoglycanopathies, congenital muscular atrophies.

Abbreviations: LMN, lower motor neuron; SMA, spinal muscular atrophies.

- Molecular genetic markers—DNA markers of hereditary myopathies, including the muscular dystrophies and neuropathies are available from leukocytes in blood samples. If it provides the diagnosis, invasive investigations such as a biopsy are not needed
- Nerve conduction velocity (NCV)
- Electromyography
- Muscle biopsy—this is the most important and specific diagnostic test of most neuromuscular disorders, if the definitive diagnosis of a hereditary disease is not provided by molecular genetic
- Testing in blood. Not (most vital)
- Nerve biopsy (usually sural nerve biopsy)
- Electrocardiography
- Serial pulmonary function tests
- Complete cardiac work-up, including echocardiography and consultation with a pediatric cardiologist in some cases.

Multiple Choice Questions

- Components of the motor unit include each of the following, except:
 - Motor neuron in brain cell or anterior horn cells of the spinal cord
 - Peripheral nerve
 - Neuromuscular junction and muscle fibers innervated by a single motor unit
 - All of the above
- Spot the wrong observation about neuromuscular disorders:
 - Cerebral palsy is included under the umbrella of neuromuscular disorder
 - Spinal muscular atrophy is the second most common neuromuscular disorder after Duchenne muscular dystrophy
 - Symmetric, ascending, rapidly progressive and predominantly motor paralysis are hallmark of Guillain-Barre syndrome
 - Benign congenital hypotonia is characterized by extreme hypotonia without delay in motor development
- Spot the wrong matching:
 - Proximal weakness, bulk relatively preserved, reflexes relatively preserved—Predominantly muscle disease-muscular dystrophies
 - X-linked recessive inheritance—Duchenne muscular dystrophy

contd...

- C. Autosomal dominant—Facioscapulohumeral dystrophy
- D. Autosomal recessive—Becker muscular dystrophy
- 4. All of the following statements are incorrect, except:
 - A. Majority of the polyneuropathies exhibit proximal-to-distal gradient of manifestations
 - B. Bell's palsy is an upper motor neuron type lesion
 - C. Gowers' sign is pathognomonic of Duchenne muscular dystrophy
 - D. "Rag-doll" position on ventral suspension is characterization of floppy infant syndrome
- 5. Each of the following is an autonomic neuropathy, except:
 - A. Familial dysautonomia and Hirschsprung disease
 - B. Reflex sympathetic dystrophy
 - C. Congenital insensitivity to pain and anhidrosis
 - D. Drug-induced myopathy

Answers

1. D 2. A 3. D 4. D 5. D

Clinical Problem-solving**Review 1**

In a class there are 7 girls, aged-13-years, presents with generalized weakness, especially gradually increasing weakness of the hands and arms on combing hair. The weakness is aggravated on repetitive movements and regresses on rest. During periods of stress, the weakness becomes more pronounced.

1. What is your diagnosis?
2. How to confirm the diagnosis?
3. Can such a patient have muscle paralysis under certain circumstances?
4. What is its treatment?

Review 2

A 16-year-old obese boy with type 2 diabetes, suffers from moderate persistent asthma with good response to introduction of oral prednisolone and montelukast in existing therapy. After a few months therapy, he presents with a new development, i.e. extreme weakness of the proximal skeletal muscles.

1. What is in your opinion, the likely cause of muscle weakness in this case?
2. What could be the probable modus operandi of such a myopathy?
3. Any risk factors that can predispose to myopathy?

Answers**Review 1**

1. Juvenile myasthenia gravis is seemingly the diagnosis in this adolescent girl.
2. Clinical diagnosis is confirmed by:
 - (a) Edrophonium/ neostigmine test
 - (b) Electric testing of neuromuscular transmission
3. Yes, when the patient is under acute stress (say psychological tension, pressure of work, surgical intervention), she may suffer from exacerbation of the condition, the so-called "myasthenic crisis". Occasionally, in a very severe form of the disease, generalized muscle paralysis may occur.
4. Treatment is in the form of anticholinesterase agents such as pyridostigmine, neostigmine or ambenonium. With this life-long therapy, most patients can lead a normal life life-long therapy. In fact, 25% of the patients may have complete cure.

Review 2

1. The most likely cause of this boy's weakness is the proximal skeletal muscles appears to be chronic steroid therapy – the so-called "steroid-induced myopathy".
2. During chronic steroid therapy, vitamin D deficiency is likely to get accentuated, contributing to steroid myopathy, especially in the presence of type 2 diabetes. If the patient's diabetes is insulin resistant, chance of developing steroid-induced myopathy is enhanced.
3. Patients with diseases such as nephritic syndrome, asthma, juvenile idiopathic arthritis, dermatomyositis, SLE, leukemias, and other autoimmune or inflammatory diseases in which chronic steroid therapy is often given are at considerable risk of myopathy.

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2. Houffin Debarge V, Delsalla A, Subtil D, et al: Fetal cells in the maternal blood: A step towards noninvasive prenatal diagnosis. *J Gynecol Obstet Biol Reprod Paris* 1998;27:483–493.
3. Kulkarni ML. Muscular dystrophies. In: Gupte S (ed): *Recent Advances in Pediatrics-10*. New Delhi: Jaypee 2000:60–84.
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1. Gupte S. *Recent Advances in Pediatrics (Special Vol. 18: Pediatric Neurology)*. New Delhi: Jaypee 2008.
2. Hoffman AE. *The Floppy Child*. London: Smith and Smith 2014.

SECTION 6

Allied Specialties

Section Outline

- 43. Pediatric Ophthalmology
- 44. Pediatric Ear, Nose and Throat (ENT) Problems
- 45. Pediatric Dental Problems
- 46. Pediatric Surgery
- 47. Pediatric Orthopedics

DEVELOPMENTAL ASPECTS

Cornea of the neonate is around 10 mm in diameter that reaches 12 mm (the adult size) in 2 years. The neonate eye is however only two-thirds of the adult size. Though perfectly clear in normal neonates, cornea may be slightly hazy in prematures. The lens is more spherical and has greater refractive index to make up for the shortness of his eye. The pupils are small, difficult to dilate and often reveal anterior vascular capsule remnants as cobweb-like lines crossing the aperture, in premature infants in particular. Because of its thinness, sclera is bluish in color. Transient conjunctival hemorrhages may be seen.

The fundus of the neonate is less pigmented, often showing prominent vascular pattern and peppery or mottled appearance of retinal pigmentary pattern. The foveal light and other macular landmarks are poorly defined. The peripheral retina is particularly pale. Transient superficial retinal hemorrhages may be encountered. Appearance of fundus tends to come close to that of the mature eye by the age of 4–6 months.

Generally, the neonate's eye is hypermetropic (farsighted); though most prematures are myopic with some astigmatism. Inclined to keep eyes closed most of the time, he is capable of seeing, reacting to changes in light, and fixating points of contrast. The visual acuity (VA) of 20/40 tends to reach 20/30 to 20/20 by the age of 2–3 years. He evince more sustained interest in large objects by 2 weeks and can follow an object through an arc of 180° by the age of 8 to 10 weeks.

The imperfect coordination of eye movements and alignment give way to proper coordination by 3–6 months. On account of poor development of the lacrimal glands, tears often make their appearance on crying after 1–3 months of age.

ORBITAL DISEASES

Hypertelorism

It refers to increased distance between pupils so that eyes are set widely apart. The cause is congenital overdevelopment of the lesser wings and underdevelopment of the greater wings of the sphenoid. It may be found in its mild form in normal individuals. Significant hypertelorism is, however, associated with mental retardation and other congenital anomalies (Fig. 43.1). It may occur as a part of certain syndromes such as Apert syndrome, Crouzon syndrome, Ehler–Danlos syndrome, craniocleidodysostosis and certain sex chromosomal anomalies.



Fig. 43.1: Hypertelorism. Note the increase in interpupillary distance.

Presence of flat nose, especially with epicanthal fold, as in Down syndrome, cretinism and Mongolian races, may give an impression of an abnormally large distance between the eyes. This is called *pseudohypertelorism*.

The most accurate measure of hypertelorism is the direct measurement of the interpupillary distance (IPD) with a caliper. This is, however, not quite practical in infants without obtaining full dilatation of the pupils under anesthesia. In clinical work-up, therefore, IPD may be derived from any of the following two equations:

$$\text{IPD} = 0.7 + 0.59 \text{ inner canthal distance} + 0.41 \text{ outer canthal distance}$$

$$\text{or}$$

$$\frac{\text{Outer canthal distance} - \text{Inner canthal distance}}{2}$$

The first equation is said to be more reliable.

After obtaining the IPD (Fig. 43.2), hypertelorism index may be calculated from the following equation:

$$\text{Hypertelorism index} = \frac{\text{Interpupillary distance}}{\text{Interorbital distance}}$$

An index exceeding 57% is indicative of hypertelorism.

Hypotelorism

Decreased IPD may be accompanied by high incidence of mental retardation, hydrocephalus and epilepsy. In addition to an isolated form, it is also seen in oculodentodigital syndrome, cyclops holoprosencephaly, and trigonocephaly (Table 43.1).

Exophthalmos (Proptosis)

The protrusion of the eye is caused by shallowness of the orbit (craniosynostosis, other craniofacial malformations)

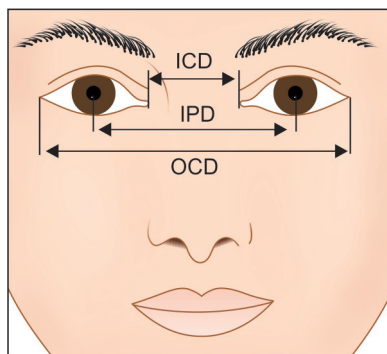


Fig. 43.2: Ocular landmarks. Presence of hypertelorism or hypotelorism is confirmed by measurement of interpupillary distance.

Abbreviations: ICD, intercanthal distance; IPD, interpupillary distance; OCD, outer canthal distance.

Table 43.1: Important causes of true hypertelorism and hypotelorism

Hypertelorism	Hypotelorism
<ul style="list-style-type: none"> • Trisomy 8 • 4p • 5p • Triploidy syndrome • Penta X, XXXX, XXXXX • Aarskog syndrome • Williams syndrome • Noonan syndrome • Fetal aminopterin syndrome • Fetal hydantoin syndrome • Fetal warfarin syndrome • Apert syndrome • Pfeiffer syndrome • Saethre–Chotzen syndrome • Roberts syndrome • Rubinstein–Taybi syndrome • G syndrome • Robinow syndrome • Weaver syndrome • Hypertelorism-hypospadias syndrome • Sotos syndrome • Larsen syndrome • Pyle disease • LEOPARD syndrome • Sjögren–Larsson syndrome • DiGeorge sequences 	<ul style="list-style-type: none"> • Trisomy 13 • Holoprosencephaly • Trigenocephaly • Oculodentodigital syndrome

by relatively increased tissue mass (cellulitis, cavernous sinus thrombosis, orbital hemorrhage, neoplasm) or by endocrinopathy (thyrotoxicosis). It may be complicated by exposure keratitis, ocular motor disturbances, optic atrophy and blindness.

Enophthalmos

The posterior displacement (sinking) of the eye back into the orbit occurs following atrophy of the orbital tissue or orbital fracture. It classically occurs in Horner syndrome (other features—ptosis, absent ciliospinal reflex, anhidrosis, miosis) which results from lesions of the lower cervical and upper thoracic sympathetic nerve fibers.

Microphthalmia

Developmentally, small eye may well be a feature of certain intrauterine infections (toxoplasmosis, rubella, cytomegalovirus) and Down syndrome. Often, it is accompanied by microcornea (anterior microphthalmia).

Orbital Cellulitis

Inflammation of the tissues of the orbit with proptosis, limitation of the eye movements, edema/swelling of the conjunctiva (chemosis) and eyelids may follow direct extension of infection involving neighboring structures (the most common being paranasal sinusitis), direct infection of the orbit, or superadded infection of an orbital tumor (metastatic or primary) (Fig. 43.3). The causative organisms, in order of frequency are *Hemophilus influenzae*, *Staphylococcus aureus*, group A beta-hemolytic streptococci and *Streptococcus pneumoniae*. The orbital cellulitis associated with paranasal sinusitis is categorized as in Table 43.2.



Fig. 43.3: Orbital cellulitis. Note the extensive pyoderma involving the face and ears. Besides inflammation of the eyelids and conjunctiva, the child had proptosis and limitation of eye movement.

Table 43.2: Staging of orbital cellulitis

Stage	Features
Stage I	Swelling limited to eyelids, some reactive periostitis
Stage II	Periosteal abscess with localized tenderness, proptosis and some limitation of eye movements
Stage III	Diffuse orbital tissue inflammation, proptosis, limitation of eye movements
Stage IV	Orbital abscess

Complications include blindness from involvement of optic nerve and cavernous sinus thrombosis, meningitis or epidural, subdural or brain abscess. Orbital cellulitis requires to be aggressively treated with systemic antibiotics plus surgical drainage of the sinus or abscess, if indicated.

Periorbital (Preseptal) Cellulitis

This term is applied to inflammation of the eyelids and periorbital tissues without evidence of true orbital involvement in the form of proptosis or limitation of eye movements. It may be the first sign of sinusitis and may progress to true orbital cellulitis. It must be treated with prompt antibiotic therapy.

Tumors

Orbital tumors may be benign (hemangioma, dermoids) or malignant (rhabdomyosarcoma, lymphosarcoma, metastatic neuroblastoma, optic glioma, retinoblastoma). **Manifestations** include proptosis, limitation of eye movements, a palpable mass, ptosis, optic nerve head congestion, optic atrophy and blindness. Detection of bruit and apparent pulsation of the globe points to a vascular lesion. **Diagnosis** is supported by ultrasonography, computed tomography (CT) scan and magnetic resonance imaging (MRI).

DISEASES OF THE EYELIDS

Ptosis

Drooping of the upper eyelid so as to cover more than 2 mm of the cornea below the upper limbus is termed **ptosis**. It may be **congenital** due to faulty development of the levator muscle or its innervating branches of the 3rd cranial nerve, or **acquired** due to myasthenia gravis. Horner syndrome, Sturge-Weber syndrome, von Recklinghausen's syndrome, injury to upper eyelid or 3rd nerve, drugs like vincristine, etc.

Congenital ptosis may be familial, transmitted as a dominant trait, and occur with a number of syndromal states such as Marcus Gunn Jaw-Winking syndrome and congenital fibrosis syndrome. Ptosis may often be accompanied by squint and/or anisometropia, eventually ending up with amblyopia. Surgical correction in mild cases should be deferred until age of 3–4 years. In moderate to severe cases, early correction to prevent amblyopia is recommended.

Lagophthalmos

Complete closure of the eyelids over the globe may be difficult because of paralysis (facial palsy involving orbicularis muscle), spasm (thyrotoxicosis), structural (scarring/atrophy secondary to burns or injury), or physiologic (during sleep). Management consists of protecting the eye by artificial tear preparations, eye ointment, moisture chambers and surgical closure of the eyelids (tarsorrhaphy).

Eyelid Retraction

It means that the upper eyelid rests above the upper limbus. It may be myogenic (thyrotoxicosis), neurogenic (anterior

mesencephalic involvement, hydrocephalus), meningitis, 799 or paradoxical (Marcus Gunn Jaw-Winking syndrome) or physiologic/reflective (eye popping).

Entropion

Inward turning (inversion) of the eyelid margin may be congenital or secondary to scarring from trachoma, Stevens-Johnson syndrome or some other inflammation. Inward turning of the eyelashes (trichiasis) may cause discomfort and even corneal damage. Surgical correction is often effective.

Ectropion

Outward turning (eversion) of the eyelid margin may result from scarring following inflammation, burns or trauma, weakness of the orbicularis muscle (facial palsy), or faulty development of the lateral canthal ligament (Down syndrome). It may be complicated by an overflow of tears (epiphora), maceration of skin of the eyelid, conjunctivitis, or keratopathy.

Blepharospasm

Repetitive or spastic closure of the eyelids may occur as tics or secondary to trichiasis, keratitis, conjunctivitis, foreign body, fatigue, or uncorrected refractive error. Botulinum toxin injected locally may be of value.

Blepharitis

Inflammation of the eyelid margin, either staphylococcal or seborrheic in etiology, may manifest with irritation, burning, itching, erythema and crusting or scaling of eyelid margins.

Treatment consists of daily cleansing of the eyelid margins and application of anti-staphylococcal ophthalmic ointment locally. Anti-seborrheic treatment of scalp in case of seborrheic blepharitis is warranted.

Hordeolum

Infection of the glands of the eyelid, usually due to *Staphylococcus aureus*, manifests as tender focal swelling and erythema. It may be of two types, namely:

1. **External hordeolum (stye)** when glands of Zeis or Moll is involved. Here, the abscess points at the eyelid margin, is small and superficial.
2. **Internal hordeolum** when involvement is of the meibomian glands. Here the abscess is large and points through skin or conjunctival surface. **Treatment** is frequent warm compresses, topical antibiotic applications and if necessary, surgical incision and drainage. If left untreated, hordeolum may be complicated by cellulitis. Recurrent hordeolum signals reinfection, underlying allergy or an immunologic defect.

Chalazion

Unlike internal hordeolum, chalazion is a granulomatous inflammation of a meibomian gland. The lesion is a chronic, firm, nontender nodule in the eyelid. If it does not

800 subside spontaneously and is large enough, it should be excised. Else, it may cause astigmatism by pressure on the eyeball in addition to a cosmetic defect.

Coloboma

It is a cleft-like deformity, often accompanied by a dermoid cyst, dermolipoma and extensive facial malformations (mandibulofacial dysostosis in the form of Treacher Collins syndrome). It must be surgically corrected to prevent ophthalmic complications because of exposure of the globe.

Tumors

Among the tumors of the eyelid figure nevi, hemangioma, lymphangioma, plexiform neuromas, basal cell carcinoma, squamous cell carcinoma, adenoma sebaceum and malignant lesions of xeroderma pigmentosum and Rothmund-Thomson syndrome. Tumors such as retinoblastoma, neuroblastoma and rhabdomyosarcoma may also involve the eyelids.

DISEASES OF THE LACRIMAL SYSTEM

Congenital Nasolacrimal Duct Obstruction

Dacryostenosis

Congenital nasolacrimal duct obstruction (CNLDO) occurs in 5% of the neonates due to incomplete canalization of the nasolacrimal duct with a residual membrane at the lower end of the duct at its entry into the nasal cavity.

Manifestations include excessive tearing, ranging from wetness of the eye to frank overflow of tears (epiphora), accumulation of mucoid or mucopurulent discharge, crusting, erythema and maceration of the skin and, in some instances, reflux of fluid or discharge on massaging the nasolacrimal sac. Differential diagnosis is from intraocular inflammation, glaucoma, or external irritation from a foreign body or corneal abrasion.

Treatment consists of giving nasolacrimal massage, 2–3 times/day, along with cleansing of the eyelids with warm water. In case of significant mucopurulent discharge, topical antibiotics are indicated. This conservative regimen resolves the problem by the age of 1 year. In case of failure of this treatment, probing is indicated. Probing may have to be repeated once or twice. A very small proportion of subjects failing to respond to repeated probing, need placement of tubes or extensive reconstructive surgery in the form of dacryocystorhinostomy.

Dacryocystitis

Frank inflammation of the lacrimal sac may occur as a complication in CNLDO. The sac area becomes swollen, red and tender. Systemic signs of infection like fever and irritability are usually present. Therapy comprises of prompt treatment with antibiotics with surgical intervention.

Alacrima (Dry Eye)

Noteworthy deficiency of tears, leading to dryness of eyes, corneal ulceration and scarring, may occur as a congenital

defect (isolated or in association with aplasia of cranial nerves, familial dysautonomia or Riley-Day syndrome, anhidrotic type of ectodermal dysplasia, glucocorticoid deficiency), or secondary to inflammation, Stevens-Johnson syndrome, dehydration, etc.

Treatment consists of frequent instillation of an artificial tear preparation. In case of unsatisfactory response, occlusion of the lacrimal puncta and even tarsorrhaphy may be carried out for protecting the cornea.

CONJUNCTIVAL DISEASES

Conjunctivitis

Inflammation of conjunctiva, as a reaction to a wide variety of agents, may be infectious or noninfectious.

Infectious conjunctivitis may be caused by viruses (measles and other exanthemata, adenovirus type 8) or bacterial (*Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Chlamydia*, *Pseudomonas*, *Streptococcus pneumoniae*, *Staphylococcus*, *Streptococcus*, *Corynebacterium diphtheriae*).

Noninfectious conjunctivitis may occur as a reaction to allergens (endogenous: phlyctenular, exogenous: vernal/spring catarrh) (Fig. 43.4), irritants/toxins (chemical conjunctivitis from silver nitrate, household cleaning agents, sprays, smoke, smog, industrial pollutants), and systemic diseases (Reiter's disease, Stevens-Johnson syndrome). Ophthalmia neonatorum (neonatal conjunctivitis) is described in Chapter 17 (Neonatology).

Subconjunctival Hemorrhage

Bright or dark-red hemorrhages in bulbar conjunctiva, of varying shape and size, may be encountered as a result of violent coughing (pertussis), sneezing, injury, inflammation or blood dyscrasia (leukemia, scurvy, idiopathic thrombocytopenic purpura).

Chemosis

Conjunctival edema/swelling may occur in orbital cellulitis, cavernous sinus thrombosis, angioneurotic edema, urticaria and acute nephritis.



Fig. 43.4: Vernal conjunctivitis. Note the marked hypertrophy and increased pigmentation of the conjunctiva at the limbus.

Pingueculum

It is somewhat raised mass on bulbar conjunctiva, usually in interpalpebral region, representing elastic and hyaline degenerative changes of the conjunctiva. No treatment is warranted.

Pterygium

It is a fleshy triangular conjunctival lesion, which classically occurs in the nasal interpalpebral region and tends to encroach on the cornea. Encroachment far onto cornea warrants surgical removal.

Dermoid Cyst/Dermolipoma

These similar lesions are smooth, elevated, round or oval, and vary in color from yellowish-white to a fleshy pink. They usually occur in upper outer quadrant of the globe.

Conjunctival Nevus

This usually a benign lesion varies in pigmentation from pale salmon patch to dark brown.

Symblepharon

This is a cicatricial adhesion between the globe and usually the conjunctiva of the lower eyelid. It follows surgery, injury (burns from acids or molten metal), or as a complication of Stevens–Johnson syndrome. Manifestations include diplopia and interference with mobility of the eyeball. Surgical separation of the adhesion is warranted.

CORNEAL DISEASES

Megalocornea

A cornea of more than 13 mm diameter, often familial and associated with other developmental disorders (osteogenesis imperfecta, Marfan syndrome), is usually accompanied by refractive errors. In adults, there is high incidence of glaucoma, subluxation of lens and premature development of cataracts. Differential diagnosis is from pathologic corneal enlargement from glaucoma.

Microcornea (Anterior Microphthalmia)

An abnormally small cornea may be familial or a feature of a developmentally microphthalmic eye. Colobomata, congenital cataract, glaucoma, aniridia and microphakia are the associated defects.

Keratoconus

Cone-shaped cornea as a result of its thinning and bulging at the center occurs either sporadically or in association with atopy, Marfan syndrome, Down syndrome and retinitis pigmentosa. Hard contact lenses and sometime, corneal transplantation may be needed.

Sclerocornea

A sclera-like vascularized and ill-defined tissue, usually at the periphery, replaces the normal translucent cornea. It generally occurs in association with other ocular anomalies and CNS, chromosomal and skeletal defects.

Dendritic Keratitis

The branching tree-like lesion, due to herpes simplex virus, is accompanied by conjunctivitis, pain, photophobia, tearing and blepharospasm. Topical 5-iodo-2-deoxyuridine (IDU) is the treatment of choice.

Interstitial Keratitis

Inflammation of corneal stroma, usually secondary to syphilis and less often tuberculosis or leprosy, manifests with pain, photophobia, tearing circumcorneal congestion and hazy cornea. Eventually, it ends up as corneal vascularization and opacities.

Phlyctenules

(Phlyctenular Keratoconjunctivitis)

Small, yellowish, somewhat raised lesions, located at the limbus and encroaching onto cornea, often with an ulcer at the advancing head, may well be an allergic reaction to tuberculin protein. In some cases, it may be associated with staphylococcal infection. A strong immunologic factor appears to be in operation. Response to topical steroids is gratifying.

Corneal Ulcers

Corneal ulcers may result from trauma (foreign body), malnutrition (xerophthalmia), adjoining ophthalmic infection (conjunctivitis, dacryocystitis), exposure (exophthalmos, lagophthalmos), diminished sensations (Riley–Day syndrome), exanthemata, or metabolic disorders (tyrosinemia).

Manifestations include corneal haziness, hyperemia, eyelid edema, pain, photophobia, tearing and blepharospasm. Pus may accumulate in the anterior chamber (hypopyon).

Pathogens causing corneal ulcers include *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae* and some fungi. Prompt treatment, both local and systemic, with attention to causative factor(s) is warranted to safeguard against blindness.

Peters Anomaly

This is a congenital corneal opacity (leukoma) with corresponding defects in the anterior chamber and iris.

PUPILLARY AND IRIS ABNORMALITIES

- **Aniridia**, meaning iris is only rudimentary, may be isolated (AN-1), associated with Wilms' tumor, genitourinary anomalies, mental retardation (AN-2), or accompanied by cerebellar ataxia, congenital cataracts, and mental retardation (AN-3).
- **Iris coloboma** is a developmental hole, notch or defect in the iris, that may occur alone or together with other coloboma or other anomalies.
- **Congenital microcoria/miosis** is the absence/defect of dilator pupillae muscle, resulting in a very small pupil that does not easily dilate.

- 802 ■ Congenital mydriasis** is the dilated pupil with poor constriction reaction to light, near gaze and miotic agents.
- **Dyscoria**, meaning abnormal shape of pupil, and corectopia, meaning abnormal pupillary position (eccentric), may occur as congenital anomalies or secondary to trauma.
 - **Anisocoria**, meaning inequality of the pupils may occur as a normal variation in healthy children or secondary to local causes (adhesions or synechiae, coloboma, aniridia), neurologic causes (sympathetic or parasympathetic lesions), or drugs.
 - **Persistent pupillary membrane** is persistence of remnants of pupillary membrane (which normally disappears before birth) as weblike strands resembling spokes of a wheel in the pupil. It may interfere with vision.
 - **Heterochromia** denotes difference in color of the two irides (heterochromia iridum) or of parts of the same iris (heterochromia iridis). It may occur as a congenital defect (Waardenburg syndrome) or from trauma, hemorrhage, inflammation, retinoblastoma, foreign body, glaucoma, iris atrophy and Horner syndrome.
 - **Dilated fixed pupil** is due to mydriatic drugs (atropine), internal ophthalmoplegia (central or peripheral lesions), transtentorial herniation (Hutchinson's pupil), ocular trauma, iridoplegia or cholinergic supersensitivity of the sphincter (tonic pupil).
 - **Constricted pupil** is due to miotic drugs (pilocarpine, opium), barbiturate, pontine hemorrhage or Horner syndrome.
 - **Rhythmic dilatation and constriction of pupil** (hippus), a normal phenomenon in some individuals, may be secondary to retrobulbar neuritis.
 - **Leukocoria** (Cat's eye reflex, white pupil) may be secondary to cataract, persistent hyperplastic primary vitreous, cicatricial retinopathy of prematurity (ROP), retinal detachment, retinoschisis, larval granulomatosis, retinoblastoma, vitreous hemorrhage, leukemia, exudative retinopathy, phakomatosis, etc.

DISEASE OF LENS

Cataracts

Cataract means an opacity of the lens. Table 43.3 categorizes a wide number of conditions responsible for pediatric cataracts. **Treatment** is addressed to surgical removal of lens, correction of resultant aphakia, and correction of accompanying amblyopia.

Ectopia Lentis

Displacement of the lens, complete (luxation) or partial (subluxation), may accompany such systemic disorders as Marfan syndrome, homocystinuria, Weill-Marchesani syndrome, sulfite oxidase deficiency, Ehlers-Danlos syndrome, Sturge-Weber syndrome, Klippel-Feil syndrome, Crouzon syndrome, oxycephaly and mandibulofacial dysostosis.

Symptoms include blurring of vision, diplopia, refractive errors and tremulousness of the iris (iridodonesis).

Treatment depends on type of displacement, its cause and the presence of ocular or systemic complications. Often, the best treatment is surgical removal of the lens.

DISEASE OF THE UVEAL TRACT

- **Iridocyclitis**, inflammation of iris and ciliary body, manifests as pain, photophobia and lacrimation. It usually accompanies pauciarticular rheumatoid arthritis, Kawasaki disease and sarcoidosis. It may also follow trauma or infective conditions in the vicinity.
- **Chorioretinitis**, inflammation of posterior portion of uveal tract may result from toxoplasmosis, histoplasmosis, cytomegalovirus, sarcoidosis, syphilis, tuberculosis and toxocariasis.
- **Panophthalmitis**, inflammation of the whole eye, usually follows a perforating injury or septicemia.

EYE MOVEMENT AND ALIGNMENT DISEASES

Strabismus (Squint)

Strabismus (Greek word, meaning, to look obliquely) occurs in some 4% of preschool children and is an important cause of visual impairment. **Orthophoria** is the ideal state of perfect oculomotor balance.

Heterophoria means that the eye deviates only under certain situations like fatigue, illness, stress, or when one eye is covered. **Heterotropia** means that the eye deviation is apparent (not latent as in heterophoria) and does not need any special situation.

Clinical Types

Two major categories are recognized nonparalytic and paralytic.

1. **Nonparalytic strabismus (concomitant)** accounts for a vast majority of the cases of strabismus. Here, individual extraocular muscles are normal. The deviation is secondary to visual or ocular defects in the involved eye.
2. **Paralytic strabismus (non-concomitant)** is due to a palsied or paretic eye muscle(s). Manifestations include diplopia, limitation of movements, false orientation of the visual field and dizziness. It may be **congenital** (neuromuscular anomalies, birth injury) or **acquired** (trauma causing fracture of the base of the skull, CNS infections, CNS tumors, encephalitic form of poliomyelitis, toxins from diphtheria, lead, botulism, thiamine deficiency).

Third, fourth and sixth nerve palsies may well be congenital or acquired. Third and fourth nerve palsies are usually congenital whereas sixth nerve palsy is only rarely congenital. The term, **strabismus syndromes**, refers to special forms of strabismus with unusual clinical features. These are usually caused by structural anomalies of extraocular muscles or tissues in their vicinity. When a monocular elevation deficit in both abduction and adduction occurs, the condition is called **double elevator palsy**.

Diagnostic Tests

Corneal light reflex tests are the simplest, easiest and fastest diagnostic tool for strabismus. The **Hirschberg test**

consists of projecting a small light onto the corneas of both eyes simultaneously and observing the reflection in each cornea as the child looks straight ahead. In a normal eye, the reflection appears centered. In an affected eye, the reflection appears off-center.

The **Krimsky test** consists of employing prisms over the eye(s) and determining the amount of prism needed to align the reflections. This amount provides the degree of deviation in the squinting eye. **Cover tests** consist of the cover-uncover test and the alternate cover test. For the first test, the child is asked to look at a distant object (about 20 feet away). Then, the examiner covers one eye and observes the movements of the other eye. If no movement is noticed, the uncovered eye is by and large normal. The procedure is repeated on the other eye.

In alternate cover test, each eye is rapidly covered and uncovered. In case of strabismus, the affected eye shows movements as the cover is shifted to the other eye. The cover tests must be performed for both distant and near visions and in all cardinal positions of the gaze with and without spectacles.

Treatment

It consist of correcting the refractory errors, cataracts, etc. If the strabismus persists despite this, occlusion therapy should be instituted. This consists in totally occluding the normal eye for a week or two to allow the affected eye to improve vision by continuous exercise.

Orthoptic treatment involves special visual exercises. Surgery is indicated if the child fails to respond to the aforesaid measures. It involves shortening, lengthening or repositioning of the eye muscles. As and when indicated, surgery must not be delayed.

REFRACTIVE ERRORS

A state of refractive error(s) is termed **ametropia** against the ideal optical state, **emmetropia** in which the parallel rays of light come to focus on the retina with the eye in a state of rest.

Hypermetropia (Hyperopia)

Farsightedness occurs when the parallel rays of light are focused behind the retina on account of too short anteroposterior diameter of the eye, subnormal refractive power of the cornea or lens, or posterior dislocation of the lens. If the error is severe, greater accommodative effort may cause blurring of vision, eye strain, headache, fatigue, convergent strabismus, eye-rubbing and eyelid inflammation. Convex lenses correct the error.

Myopia

Shortsightedness occurs when the parallel rays of light come to focus in front of the retina on account of the too long anteroposterior diameter of the eye, higher refractive power of the cornea or lens, or anterior dislocation of the lens. The major symptom is blurred vision for distant objects. The myopic child has difficulty in reading the blackboard and pursuing the distant activities. He tends

to keep the book and other reading/writing matter close to his eyes. Frowning and squinting result from child's inclination to improve the visual activity by reducing the eyelid aperture. Concave lenses correct the error.

Astigmatism

It means there is difference in the refractive power of different meridians of the eye, usually because of the irregularity in the curvature of the cornea or lens. As a result, parallel rays of light fail to come to focus at a point. Astigmatism may be complicated by amblyopia.

Significant astigmatism leads to distortion of images, frowning, squinting, eyestrain, headache, fatigue, eye-rubbing, eyelid hyperemia, indifference to schoolwork, and holding reading matter close. Conditions predisposing to astigmatism are ocular trauma, periorbital and eyelid hemangioma and ptosis. Cylindrical or spherocylindrical lenses correct the error.

Anisometropia

Difference in the refractive states of the two eyes may cause **amblyopia** or **lazy eye**. Early correction is warranted.

Impairment/Paralysis of Accommodation

It may result from premature presbyopia, overuse of cycloplegic substances (anticholinergics, poisons), 3rd cranial nerve lesions, botulism, diphtheria, Wilson disease, diabetes mellitus, syphilis, viral infections, feigning (psychogenic), etc. Congenital inability to accommodate, though rare, is known.

VISUAL DISORDERS

- **Amblyopia** means subnormal vision in one or both eyes in spite of correction of significant refractive error. The most important cause is sensory stimulation deprivation during the early developmental life (sensory deprivation amblyopia).
- **Amaurosis** means partial or total loss of vision in the form of profound impairment, near-blindness, or blindness. It may follow developmental malformations, gestational/perinatal infections, anoxia/hypoxia, perinatal trauma, and certain genetic disorders. If it develops in a child who once had good vision, the etiology factors may be an ocular disease, encephalopathy, vasculitis, migraine, leukemia, toxins, trauma, infectious or post-infectious processes, demyelinating diseases, rapidly rising intracranial pressure (ICP), dysfunction of a shunt, craniopharyngioma, neurodegenerative disease, tumors, gliomas of optic nerve or chiasm, etc. Accompanying manifestations include strabismus, nystagmus, timidity, clumsiness, behavioral changes, deterioration in school performance and shirking participation in school activities.
- **Night blindness (nyctalopia)** may be congenital or acquired (xerophthalmia, quinine and other retinotoxic drugs, retinal, choroidal or vitreoretinal degeneration).

- 804 ■ Diplopia**, meaning double vision, usually occurs in strabismus and in proptosis. It may be a warning sign for the ensuing raised ICP, a brain tumor, an orbital mass or myasthenia gravis. Monocular diplopia points to existence of dislocated lens, or a defect in the media or the macule.
- **Psychogenic vision problems**, both malingering and conversion reaction, may be complained of the school going children.
 - **Dyslexia** means a specific reading disability due to a primary or developmental defect in the higher cortical processing of graphic symbols. The associated symptoms include letter or word reversal and mirror writing. An ophthalmologic evaluation is warranted. Treatment is directed at remedial instruction and counseling of the child and the family.

DISEASES OF THE RETINA AND VITREOUS

Retinopathy of Prematurity (Retrolental Fibroplasia)

Etiopathogenesis

Prematurity (<33 weeks), retinal immaturity and hyperoxia are the major etiologic factors. Sickness of the neonate (respiratory distress, apnea, bradycardia, infection, anemia, heart disease, hypoxia, hypercarbia, acidosis and need for transfusion) is a contributory factor.

The first landmark in its pathogenesis is cessation of vasculogenesis. A line marks the abrupt termination of vascularized to the avascular retina. The line changes into a ridge and vascularization of retina may proceed, or an abnormal proliferation of vessels out of the plane of the retina into the vitreous, over the surface of retina, ciliary body and lens. Finally, cicatrization and traction on retina may cause retinal detachment.

Classification

Five stages of ROP are now recognized (Table 43.4).

Treatment

Early diagnosis followed by cryotherapy to the avascular retina prevents further progression of retinopathy. In advanced cases (stage V), sophisticated vitreoretinal surgery may successfully reattach the retina.

Table 43.4: International classification of retinopathy of prematurity

Stage	Features
Stage IA	Demarcation line between the vascularized and avascular retina.
Stage IIA	Ridge in place of the line.
Stage IIIA	Ridge plus extraretinal fibrovascular tissue.
Stage IVA	Subtotal retinal detachment.
	Phase I—when macula is spared. Phase II—when macula is involved.
Stage V	Total retinal detachment.

Prevention

This lies in prevention of prematurity, judicious use of oxygen and supplemental vitamin E as an antioxidant in high-risk infants.

RETINOBLASTOMA

Already detailed in Chapter 33 (Pediatric Oncology).

Retinitis Pigmentosa

This is a type of progressive retinal degeneration characterized by pigmentary changes, narrowing of retinal arteries, optic atrophy and impaired visual function.

It may be primary or secondary to intrauterine infections (toxoplasmosis, other agents, rubella, cytomegalovirus and herpes simplex/syphilis {TORCH, STORCH}), mucopolysaccharidosis, late-onset gangliosidoses, abetalipoproteinemia, progressive retinal ophthalmoplegia, drugs (chloroquine, phenothiazines), Laurence-Moon-Biedl syndrome, Usher syndrome, Refsum syndrome, hereditary ataxia and Alport syndrome.

Manifestations include difficulty in dark adaptation, progressive loss of peripheral followed by central vision and reduced retinal function as measured by electroretinography.

Retinal Detachment

It means separation of outer layer of retina from the underlying retinal pigment epithelium. It may be primary or secondary.

Secondary retinal detachment is of three types—(1) rhegmatogenous detachment (trauma as in child abuse, myopia, ROP, congenital cataract surgery) is the result of a break in the retina that allows fluid to enter the subretinal space; (2) tractional detachment (diabetes mellitus, sickle-cell disease, retinopathy) follows pull of the vitreoretinal membrane on the retina; (3) exudative detachment (retinoblastoma, ocular inflammation, Coats' disease) results from exudation exceeding absorption.

Manifestations include loss of vision, strabismus, nystagmus, white pupillary reflex (leukocoria). **Diagnosis** is established by ultrasonography, CT scan and MRI.

Hypertensive Retinopathy

Detection of hypertensive retinal changes is a clue to existence of renal disease, pheochromocytoma, cardiovascular disease (coarctation of the aorta in particular) or collagen disorder.

Diabetic Retinopathy

Early (nonproliferative) diabetic retinopathy is characterized by microaneurysms, venous dilation and hemorrhages and exudates.

Late or more advanced (proliferative) diabetic retinopathy is characterized by neovascularization and proliferation of fibrovascular tissue extending on to the vitreous and vision threatening complications like vitreous hemorrhages, cicatrization, traction, and retinal detachment,

and rubeosis of the iris and secondary glaucoma. It occurs in only 20–25% diabetic children before 10 years and in as high as 50–60% after 20 years of known disease. Adequate control of the diabetic state helps in postponing diabetic retinopathy. Ocular therapy in the form of retinal photocoagulation and vitrectomy contributes to reduce morbidity.

OPTIC NERVE DISEASES (FIGS 43.5 TO 43.9)

Papilledema (Choked Disk)

The term denotes the noninflammatory passive edema of the optic disk secondary to increased ICP from such causes as intracranial space-occupying lesion (ICSOL) like tumors, obstructive hydrocephalus, intracranial hemorrhage, meningoencephalitis, toxic encephalopathy, conditions with early closure of sutures and fontanel (craniosynostosis) and pseudotumor cerebri.

The optic disk changes include edematous blurring of the optic disk margins, fullness of the nerve head, partial or complete obliteration of the physiologic cup, capillary congestion and hyperemia of the nerve head, generalized engorgement of the veins, loss of spontaneous venous pulsation, nerve fiber layer hemorrhages around the

disk and peripapillary exudates. Additional features in some cases include extension of edema onto the macula leading to star-shaped or fan-shaped figure formation, and concentric peripapillary retinal wrinkling.

Though papilledema resolves following relief of raised ICP, disk takes 6–8 weeks to revert to normal. Long-stand-

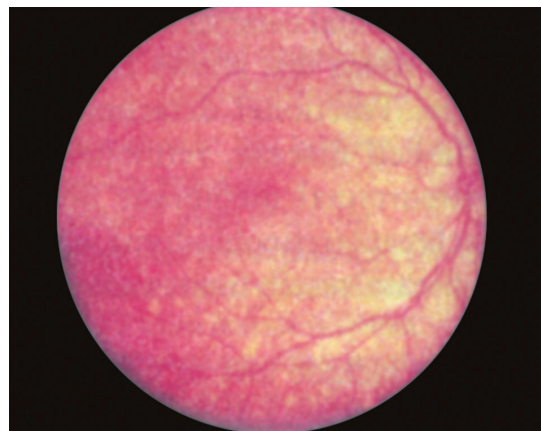


Fig. 43.7: Fundus in congenital rubella. Note finely dispersed dark and light pigmentation, especially in the region of the posterior pole.

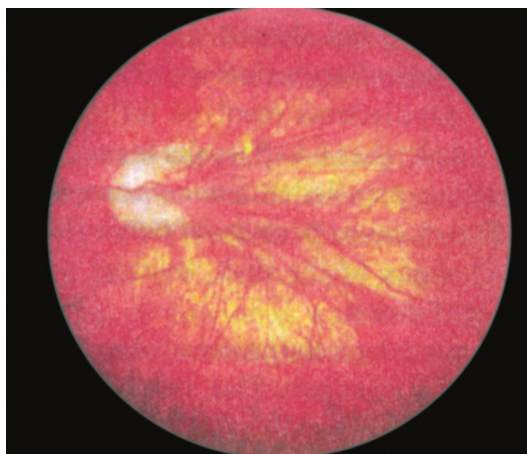


Fig. 43.5: Fundus in retinopathy of prematurity. Note beginning of vascular traction of the optic disk toward the temporal periphery.

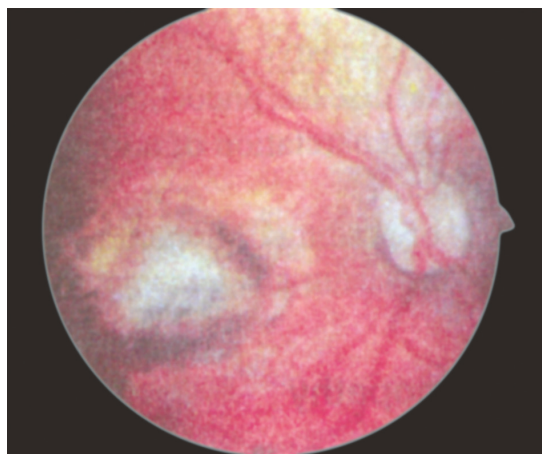


Fig. 43.8: Fundus in congenital toxoplasmosis. Note the large atrophied area of macula with abundant pigmentation at the edges suggesting choroidoretinitis.

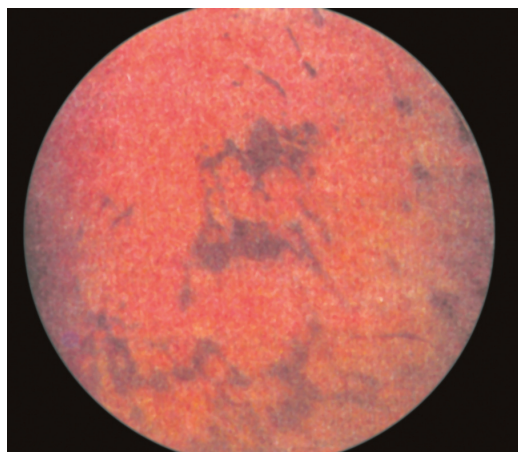


Fig. 43.6: Fundus in retinopathy of prematurity. Note the remarkable pigment changes.

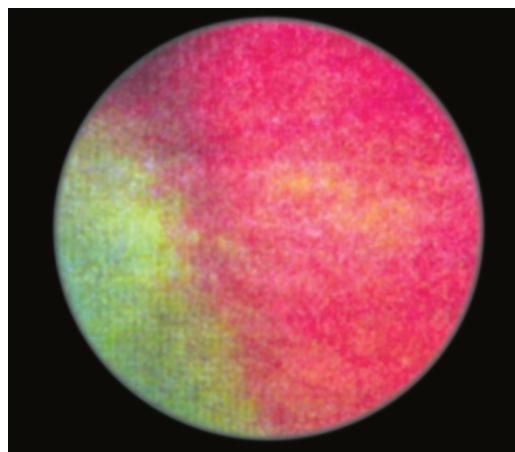


Fig. 43.9: Fundus in retinopathy of prematurity. Note fibrovascular proliferation on the margin of retina in the region of temporal periphery.

806 ing papilledema accompanying chronic raised ICP may cause permanent nerve fiber damage, atrophic changes of the optic disk, nuclear scarring and impairment of vision. Lumbar puncture in the presence of papilledema must only be done by an expert. Else, it may cause coning and death.

Optic Neuritis

The term is applied to inflammation, demyelination or degeneration of the optic nerve with impairment of its function. When optic neuritis restricts to retrobulbar portion of the nerve without any changes in the fundus, it is termed **retrobulbar neuritis**.

When the changes are detectable at the fundus ophthalmoscopically, it is termed **papillitis** (intraocular optic neuritis). When involvement is of both of retina and papilla, it is termed **optic neuroretinitis**.

The **etiologic factors** include bacterial meningitis, encephalomyelitis following an exanthem, demyelinating diseases, drugs/toxins (chloramphenicol, vincristine, ethambutol, phenothiazines, quinidine, lead). **Treatment** is with high doses of systemic steroids. Most cases begin to respond in 1–4 weeks, the vision reverting to normal in weeks or months. Permanent impairment of vision may occur in some instances.

Optic Atrophy

This refers to irreversible degeneration of the optic disk, which develops remarkable pallor with reduction in number of capillaries below 7 against the normal 10 or more and the loss of substance of the nerve head.

Primary optic atrophy denotes occurrence of atrophy without previous ophthalmoscopic evidence of papilledema/

papillitis. It follows involvement of neurons proximal to the disk. Disk margins are well defined.

Secondary optic atrophy denotes occurrence of atrophy with previous evidence of papilledema/papillitis. It involves the choked disk. Disk margins are poorly defined. **Etiologic factors** include intracranial tumors and traumatic, inflammatory, vascular and degenerative disorders. At times, progressive optic atrophy is hereditary.

SYSTEMIC MEDICATION AND OCULAR DAMAGE

In this connection, two drugs need a special mention:

1. **Chloramphenicol**, when consumed over a prolonged period, may cause optic neuritis, most often retrobulbar neuritis. Withdrawal of the drug usually leads to complete recovery.
2. **Corticosteroids** may cause two problems, namely:
 - Subcapsular cataract, following high doses, say 15–20 mg, of prednisone daily over a span of 2 years or so.
 - Glaucoma (secondary in susceptible children).

OCULAR TRAUMA

- A simple blunt trauma may cause just what is termed **black eye**.
- A penetrating injury can be dangerous.
- A detailed history from parents/attendants is important. It is advisable that the pediatrician seeks assistance from an ophthalmologist who may prefer to examine the child in operation theater under mild sedation to ascertain the nature and extent of the damage to the ocular structures.

Multiple Choice Questions

1. Each of the following observations about developmental aspects of ophthalmology is true, except:
 - A. Neonatal cornea is about 5 mm in diameter
 - B. Haziness of cornea in premature infants is a normal finding
 - C. Neonate's eye is generally hypermetropic
 - D. Tears often make their appearance on crying only after 1–3 months of age
2. True hypertelorism occurs in each of the following, except:
 - A. Apert syndrome
 - B. Down syndrome
 - C. Noonan syndrome
 - D. Fetal hydanotin syndrome
3. Dry eye is a feature of each of the following, except:
 - A. Familial dysautonomia
 - B. Anhidrotic ectodermal dysplasia
 - C. Dehydration
 - D. Chalazion
4. Megalocornea may be seen in:
 - A. Patau syndrome
 - B. Turner syndrome
 - C. Marfan syndrome
 - D. Gigantism

contd...

5. Spot the wrong statement:
- A. Orthophoria is the ideal state of perfect oculomotor balance
 - B. Lumbar puncture in the presence of papilledema may cause coning and death
 - C. Cefixime, when consumed over a prolonged period, causes optic neuritis
 - D. Intraocular optic neuritis is just another name for papillitis

Answers

1. A 2. B 3. D 4. C 5. C

Clinical Problem-solving

Review 1

A 6-week-old healthy infant, weighing 4.5 kg, presented with excessive tearing of right eye since age of 4 weeks. It has become worse in the past few days. Now, there is a slight mucopurulent discharge too. On pressing the nasolacrimal sac area, frank discharge becomes obvious.

1. What is the likely diagnosis?
2. What is its cause?
3. What is its treatment?
4. What if the treatment fails?

Review 2

A school-going boy, aged 7 years, on treatment for acute sinusitis with poor compliance, presents with painful swelling of the eyes with fever and malaise.

1. What is the most likely diagnosis?
2. How is this condition treated?
3. What are its complications?

Answers**Review 1**

1. The most probable diagnosis in this infant is congenital nasolacrimal duct obstruction (CNLDO).
2. The cause of CNLDO is poor canalization of the nasolacrimal duct with a residual membrane at the lower end of the duct at its entry into the nasal cavity.
3. Most cases respond to 2-3 times daily massage over the nasolacrimal area. In case of excessive discharge, lids need to be gently cleaned with warm water. Usually, in most cases resolution occurs by end of first year of life.
4. Poor response to massage over several months is an indication for "probing" which may need repetition a few times.

Review 2

1. The development of painful swelling of the eyes with fever in this child suffering from acute tonsillitis strongly suggests diagnosis of orbital cellulitis.
2. Orbital cellulitis needs an aggressive therapy with systemic antibiotics along with non-steroidal anti-inflammatory drugs (NSAIDs).
3. Complications are serious and include cavernous sinus thrombosis, involvement of optic nerve causing blindness, meningitis and brain abscess.

FURTHER READING

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INTRODUCTION

Almost one-thirds of ear, nose and throat (ENT) out-patient department (OPD) attendance is accounted by the pediatric subjects. In pediatrics per se, around one-fifth of the problems are accounted by the ENT disorders. The reasons for this high incidence of ENT problems in pediatric age group include:

- Infections that easily attack immature immune system, anatomy and physiology.
- Shorter, straighter eustachian tube with inadequate opening mechanism in the child than the adult.
- Lymphoid hypertrophy.

THE EAR DISORDERS

The complicated embryology of ear allows for a large variety of developmental malformations of pinna, external meatus, tympanic membrane, middle ear cavity and ossicles. From the point of view of congenital conductive deafness, defects in the external meatus (which prevent sound waves reaching the tympanic membrane) and abnormalities of ossicular chain (which interfere with transmission of sound to inner ear) are most important.

Congenital malformations include accessory skin tags (preauricular tags or pits may be part of syndromes such as Goldenhar syndrome, Cri du chat syndrome, Wolf-Hirschhorn syndrome Trisomy 4p), “lop” ear (abnormally prominent ear), auricle that is rudimentary (microtia) or totally absent (anotia), atresia or stenosis of the external auditory canal (usually with sensorineural hearing loss), congenital cholesteatoma which acts as a tumor and a focus of severe infection.

Acquired disorders include otitis externa, furunculosis, acute cellulitis, dermatoses, herpes simplex, herpes zoster oticus (Ramsay Hunt syndrome) and bullous myringitis, wax, and otitis media. Otitis externa (swimmer’s ear) is characterized by diffusely red and swollen ear canal, resulting in earache accentuated by manipulation of pinna and pressure on the tragus. The common etiologic agents are—*Pseudomonas aeruginosa*, *Pseudomonas species*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, *Candida* and *Aspergillus*.

Treatment consists of instillation of antibiotic plus steroid drops in most cases. Ear wax (cerumen) is a product of glandular secretions and exfoliated keratin. If in excess, when it may block the canal at any age, its removal can

usually be accomplished by softening drops, syringing, mechanical means, or a combination of these.

Foreign Bodies in the Ear

Nonliving foreign bodies often inserted into the external auditory canal include pieces of paper, chalk or eraser, grain seeds which tend to swell with passage of time and get tightly impacted.

Living foreign bodies (say insects) may find their way into the ear canal and cause intense irritation and pain. Before its removal, the insect needs to be killed by instilling spirit or chloroform water. The foreign body may be removed carefully by forceps, syringing, suction, special instruments or post-aural approach, depending on the merits of the case.

Acute Otitis Media (AOM)

The term refers to the infection of the middle ear. It is particularly common in infants and young children. Firstly, because the Eustachian tube is short, wide and horizontal and the baby tends to lie supine, thereby hindering the drainage. Secondly, upper respiratory infections (URI) are quite frequent and result in obstruction by the lymphoid tissue in these age groups. Thirdly, congestion of the gums in babies who are erupting teeth may cause spread of infection through the lymphatics of the Eustachian tube to the middle ear.

Etiology

The common etiologic organisms in order of frequency are: *Streptococcus pneumoniae*, *Hemophilus influenzae* and *Moraxella catarrhalis* (these three are responsible for 75% of the cases), *Staphylococcus aureus*, group A streptococcus, alpha streptococcus, *Pseudomonas aeruginosa* and group B streptococcus. In neonates who are hospitalized or who are under 2 weeks, Gram-negative pathogens, *Staphylococcus aureus* and group B streptococcus are most frequent. In a proportion of the cases, viral infection may be the cause. The condition is usually associated with URI respiratory infection (25% of pediatric URI cases develop it), measles, influenza or rubella.

Clinical Features

Manifestations include pain, restlessness, discharge and fever. Parenteral diarrhea and vomiting may occur. Eardrum appears lusterless, rough and red initially. Later, collection of pus causes loss of its landmarks and its bulges outwardly (Fig. 44.1). Perforation may occur,

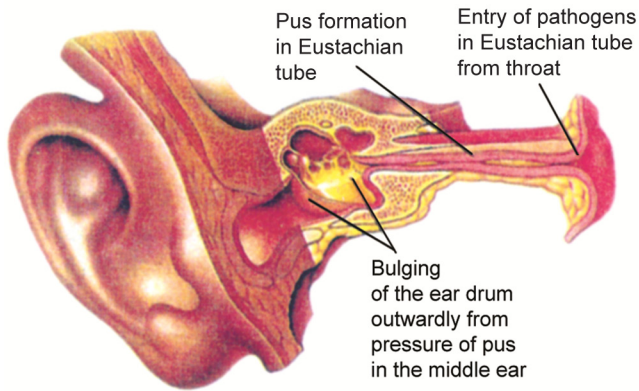


Fig. 44.1: Acute otitis media (an artist's representation).

resulting in accumulation of pus in the canal. All infants with unexplained pyrexia and/or screaming should have AOM excluded.

Treatment

Amoxicillin is the drug of choice. In view of high incidence of beta-lactamase-mediated resistance, amoxicillin-clavulanate (coamoxiclav) may be preferred. Alternative recommendations include cefaclor, cefuroxime axetil, cefadroxil, cefixime, erythromycin-sulfa combination, etc. A 10 day to 2 week therapy suffices. A single dose therapy with ceftriaxone (intramuscularly [IM]) has given equally good results.

Supportive measures include analgesics, decongestants and local heat. If there is considerably bulging of the drum with severe pain that has not responded to conservative measures, the drum may be incised under anesthesia. If the drum has already burst, the ear canal should be swabbed clean and dry repeatedly.

Prognosis

Most cases recover completely. Some may relapse quickly as soon as antibiotic is withdrawn. These children often carry a collection of sterile secretions in middle ear between acute attacks and are noted to constantly rub their ears. Treatment comprises of myringotomy and insertion of grommet tubes on a prophylactic basis.

Complications

Complications include, recurrent otitis media, perforation of the drum, acute mastoiditis with or without chronic otitis media, meningitis and cerebral abscess.

The term **otitis media with effusion** (OME) refers to the middle ear effusion lacking the clinical manifestations of acute infection like earache and pyrexia. The effusion may be serous, mucoid or purulent. No treatment is usually indicated as in 90% of cases it clears by three months after the first episode of otitis media. If the effusion persists beyond three months (chronic OME), a trial of antibiotics followed by, if needed, myringotomy with insertion of tympanostomy tubes is indicated.

Chronic otitis media is characterized by perforation of the tympanic membrane with otorrhea and hearing loss (active COM) or only hearing loss (inactive COM). The first, often termed **chronic suppurative otitis media** (CSOM),

is elimination of the infection from the middle ear and the mastoid followed by surgical repair after the age of 10 years.

Deafness (Hearing Impairment)

Children with profound more than 90 dB loss or total deafness fail to develop speech. They are often labeled **deaf-mute** or **deaf and dumb**. However, they have a normal speech-producing apparatus. Since they have never heard speech, they fail to develop it. In lesser degree of hearing loss, speech develops, but is defective. Period from birth to five years is critical for development of speech and language. Logically, therefore, early identification and assessment of hearing loss is important. Hearing loss may be congenital or acquired, temporary or permanent, of varying magnitude (mild, moderate or profound), peripheral or central in origin and organic or nonorganic.

Types

Central hearing deficit denotes auditory deficit originating along central auditory nervous system from the proximal 8th nerve to cortex (seizures, tumors, demyelinating disease, Landau syndrome).

Peripheral hearing deficit denotes dysfunction in the sound transmission through the external or middle ear as also its conversion into neural activity at the inner ear and 8th nerve. It may be conductive (impacted wax, foreign body, perforation of tympanic membrane, OME, cholesteatoma, otosclerosis, etc. blocking sound transmission in external and middle ear), sensorineural (lesion of acoustic division of 8th nerve, destruction of hair cells in inner ear) or mixed.

Etiology

Box 44.1 gives the etiology of hearing loss depending on whether it is congenital or postnatal and genetic or nongenetic.

Clinical Effects

Only some 6% of the hearing-impaired children have profound hearing loss. The rest retain some hearing. Even mild or unilateral deafness has a detrimental effect on development and performance of the child. Deafness early in life may affect the development of speech, behavior, attention, academic attainment, social development and emotional development.

Evaluation

Identification of hearing impairment is through high index of suspicion (Boxes 44.2 and 44.3).

Assessment of Hearing through Special Techniques

- Screening procedures
 - Arousal test
 - Audiometry response cradle
- Behavior observation audiometry
- Distraction techniques
- Objective tests
 - Evoked response audiometry

Box 44.1 Etiology of pediatric deafness**Congenital**• **Genetic**

- **Familial:** Familial deafness (early onset)
- **Syndromal:** Waardenburg syndrome, Pendred syndrome, Usher syndrome, Treacher Collins syndrome, Pierre Robin syndrome, Crouzon syndrome, Klippel–Feil syndrome
- **Chromosomal:** 13–15 trisomy, 18 trisomy, 21 trisomy

• **Nongenetic**

- **Drug teratogenicity:** Quinine, streptomycin, thalidomide, irradiation
- **Intrauterine infections:** Rubella, cytomegalovirus

Postnatal• **Genetic**

- **Familial:** Familial deafness (late onset)
- **Syndromal:** Hunter-Hurler syndrome, von Recklinghausen disease, Alport disease, Alström disease

• **Nongenetic**

- **Mechanical:** Blockage of the external auditory meatus
- **Infections:** Meningitis, encephalitis, measles, mumps, syphilis, recurrent otitis media
- **Drugs:** Aminoglycosides, platinum
- **Toxic:** Neonatal hyperbilirubinemia
- **Brain damage:** Cerebral palsy, mental retardation, low birth weight (under 1,500 g), severe respiratory depression, prolonged mechanical ventilation.

Box 44.2 Signals for hearing loss

- Uninterrupted sleeping though loud noises
- Failure to startle to loud sound
- Failure to develop speech at 1–2 years
- Defective speech
- Poor school performance.

Box 44.3 Risk factors for hearing loss

- Family history of hearing loss
- Prenatal infections/ototoxic drugs
- Birth weight under 1,500 g
- Stigmata of syndromic deafness (deformed pinna, cleft palate, craniofacial anomalies)
- Serum bilirubin exceeding 20 mg/dL in a neonate
- Central nervous system infections (meningitis especially due to *Hemophilus influenzae*, encephalitis)
- Hypoxic ischemic encephalopathy.

- Impedance audiometry
- Otoacoustic emissions
- Heart rate audiometry.

Treatment

Evaluation assists in arriving at the type and degree of hearing loss in most of the cases. The objective of treatment is development of speech and language and adjustment in society. Components of treatment are:

- Parental guidance
- Hearing aids which help to develop lip reading
- Development of speech and language through:
 - Auditory oral communication
 - Manual communication
 - Total communication—use of all modalities of sensory input, i.e. auditory, visual, tactile and kinesthetic.

- Education—radio-hearing aids help the child hear teacher's voice better.
- Vocational guidance.

THE NOSE DISORDERS

Congenital anomalies, usually associated with cleft palate, include choanal atresia which, if bilateral, is a neonatal emergency. Acquired nose problems include rhinitis, sinusitis, trauma, foreign body and epistaxis.

Acute rhinitis, the most common disorder of nose, manifests with mucopurulent discharge, often accompanied by sneezing, malaise and headache. It is usually viral, but bacterial rhinitis may be severe and accompanied by infection of sinuses, ear or throat. Treatment is with oral and/or local decongestants and analgesics. An antibiotic is indicated if bacterial infection is suspected as judged from its severity and persistence despite symptomatic therapy. URI are discussed in Chapter 26 (Pediatric Pulmonology) trauma may be followed by nasal obstruction, implying that either deviated nasal septum (DNS) or a septal hematoma has developed.

Foreign Body in Nose

Inanimate foreign bodies found in the nose include beads, buttons, paper, peas, erasers and metal and plastic components of toys. When retained for a long time, they produce granulation tissue.

Animate foreign bodies include maggots, leeches and other insects. Most often, history clinches the diagnosis. Else, a foul-smelling and bloodstained discharge should arouse suspicion. For its removal of inanimate foreign body, a curved hook (say, Eustachian catheter) is passed beyond the foreign body which is then pulled out.

Leeches can be removed by putting a pinch of salt or a few drops of oxalic acid on their body. Maggots can be asphyxiated with turpentine oil and then removed as they crawl out for want of oxygen.

Epistaxis (Nosebleeds)

After first year and upto puberty, about 10% of children suffer from this symptom. A vast majority of the bleeds are minor and transient, stopping spontaneously or with little local pressure. Anterior inferior part of the cartilaginous nasal septum with rich blood supply (Kiesselbach's plexus) followed by mucosa lining the anterior portion of the turbinates are the common sites of epistaxis. For details, See Chapter 26 (Pediatric Pulmonology).

Sinusitis

Acute purulent sinusitis may occurs either secondary to acute rhinitis or as an acute empyema. Chronic sinusitis suggests existence of a predisposing disorder such as DNS, polyps, adenoids, septic tooth, allergy, cystic fibrosis, dyskinetic cilia or an immunodeficiency state. For details, See Chapter 26 (Pediatric Pulmonology).

Nasal Polyps

The benign pedunculated tumors from chronically inflamed and edematous mucosa, manifest with nasal obstruction, hyponasal phonation, mouth breathing, mucoid or mucopurulent rhinorrhea and widening of the bridge of the nose. Their association with cystic fibrosis, asthma, chronic sinusitis, and chronic allergic rhinitis is well known. Treatment is surgical removal.

THE THROAT DISORDERS

Congenital anomalies include cleft palate and laryngomalacia, laryngeal webs, cysts and hemangiomas. Laryngomalacia, a frequent benign problem, manifests as inspiratory stridor within a few weeks of birth. The stridor becomes more pronounced on crying or when the infant lies supine (i.e. on his back). A benign and self-limiting condition. It gradually decreases in severity, usually subsiding by 6–12 months age acquired disorders include pharyngitis, tonsillitis, adenoids, stridor, croup syndrome (laryngitis, epiglottitis, etc.). For details, See Chapter 26 (Pediatric Pulmonology).

Diphtheria

Diphtheria is caused by *Corynebacterium diphtheriae*, a Gram-positive pleomorphic rod. It is characterized by formation of a membrane, primarily in the upper airway, along with toxemic manifestations as a result of liberation of a powerful endotoxin. Though it had become rare, in the recent years its cases are being increasingly encountered globally. For details, See Chapter 19 (Bacterial Infections).

INTUBATION AND TRACHEOSTOMY

Intubation and tracheostomy are performed for relieving the airway obstruction, facilitating bronchial toilet and assisting ventilation so that respiratory distress is either prevented or overcome. Box 44.4 gives indications for intubation and tracheostomy.

Intubation is preferred if the natural course of disease is expected to be short, usually when the cause of obstruction lies in the neighborhood of larynx. Intubation tubes are either of polyvinyl or silastic material. Silastic tubes are preferred as they are inert and cause very little tissue damage and become malleable at body temperature, thereby conforming to various contours they traverse. Usually no sedation is required.

Tracheostomy is the procedure of choice for relief of airway obstruction when intubation is not workable or when such relief is required for periods extending the safe upper limit of intubation. Usually, it is performed under general anesthesia. The incision made is a short transverse one midway between lower border of thyroid cartilage and suprasternal notch. The child with tracheostomy should be nursed in an atmosphere of moist air because warming and moistening functions of nasal mucosa have been bypassed.

Complications of tracheostomy include:

- Subcutaneous emphysema from a leak around tube
- Mediastinal emphysema and pneumothorax due to exit of the tube from trachea or extensive dissection in lower neck
- Death due to complication of operation, blockage of tube, crusts in bronchi, duplication of tube and improperly inserted tube.

In case of a tracheostomy performed for an acute condition, extubation is done within a week. In case of tracheostomy, which has been there for quite some time, intubation should be done after a soft tissue lateral radiograph to ensure that alignment of airway is not distorted.

Box 44.4 Indications for intubation and tracheostomy

- Bronchial toilet
- Respiratory distress
 - **Acute obstruction in the region of larynx:** Acute epiglottitis, foreign body
 - **Acute lower respiratory tract infection:** Acute laryngotracheobronchitis, bronchitis, staphylococcal, pneumonia
 - Edema from inflammatory causes.

Multiple Choice Questions

1. Spot the wrong observation:
 - A. Wax is a product of glandular secretions and exfoliated keratin
 - B. *Streptococcus pneumoniae* is the most common cause of acute otitis media
 - C. Central hearing defect is an auditory deficit originating along central auditory nervous system
 - D. Most frequent causative pathogen in acute epiglottitis is *Staphylococcus aureus*
2. The most appropriate entry concerning signals for hearing loss is:
 - A. Uninterrupted sleep in spite of loud noises
 - B. Failure to startle to loud sound
 - C. Defective speech
 - D. All of the above

contd...

3. Accessory skin tags may be a part of each of the following, except:
 - A. Goldenhar syndrome
 - B. Cri du chat syndrome
 - C. Crouzon syndrome
 - D. Trisomy 4p
4. Each of the following is a common etiological agent for acute otitis media, except:
 - A. *S. pneumonia*
 - B. *H. influenza*
 - C. *M. catarrhalis*
 - D. Group A streptococcus
5. Each of the following is an indication for tracheostomy/intubation, except:
 - A. Acute laryngotracheobronchitis with severe respiratory distress
 - B. Acute severe tonsillitis without respiratory distress
 - C. Acute severe epiglottitis
 - D. Bronchial toilet

Answers

1. D 2. D 3. C 4. D 5. B

Clinical Problem-solving

Review 1

A 2-year-old boy suffering from rhinorrhea presents with excessive crying, restlessness and mild diarrhea. A dose of promethazine and acetaminophen each have failed to relieve his symptoms. On the other hand, he has also become febrile too. There is no breathing problem.

1. What according to you should be the diagnosis?
2. What is its bacteriological etiology?
3. How to confirm the diagnosis?
4. What is the drug of first choice for this condition?

Review 2

A 2-year-old child, fond of playing with titbits like buttons and beads, presents with foul-smelling and blood-stained discharge from right nostril with some noisy breathing from the same side.

1. What according to you should be the diagnosis?
2. What is modus operandi of occurrence of such a problem?
3. How to treat it?

Answers**Review 1**

1. Acute otitis media (AOM) in view of the very suggestive clinical presentation. The problem is quite common in infants and young children on account of the favorable peculiarities of the Eustachian tube in them.
2. Common causative pathogens in order of frequency are—*Streptococcus pneumonia*, *H. influenza*, and *M. catarrhalis* which are responsible for 3/4th of cases.
3. Diagnosis is confirmed by characteristic appearance of the ear drum.
4. Co-amoxiclav, in view of increasing resistance to amoxicillin, is the drug of choice for AOM.

Review 2

1. The presentation with unilateral foul-smelling discharge in a toddler who plays with titbits like beads and buttons is highly suggestive of a foreign body in the nose.
2. Two types of foreign bodies cause problem in nose—usually inanimate such as beads, peas, buttons, erasers, etc. (usual) and inanimate such as maggots, leeches and other insects.
3. Treatment lies in removal of the inanimate foreign body by passing a curved hook beyond the foreign body and then pulling it out.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

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NORMAL DENTITION

Initiation of primary dentition occurs *in utero* round about 7th week of gestation when primary teeth take root in dental crypts, the latter arising from a band of epithelial cells incorporated into each developing jaw. Tooth formation in case of permanent teeth begins around 15th week of intrauterine life, the incisors being the first ones to appear followed by molars.

After the formation of matrix, it takes another 2 months for the commencement of calcification. The color, texture or thickness of the tooth surface may be influenced by disturbance of matrix formation, under or nonavailability of one of the minerals involved, or the incorporation of foreign materials. (Fig. 45.1). For time of eruption of primary and permanent teeth, See Chapter 3 (Normal Growth).

DENTAL MALOCCLUSION

The term, **malocclusion**, implies malposition and imperfect contact of the mandibular and maxillary teeth. Lack of proper relationship between upper and lower dental arches result in:

- Cosmetic disfigurement of the face
- Erroneous mastication
- Loss of teeth as the masticating or biting force is distributed from bone to tooth attachment over a much smaller area when the teeth of the upper jaw and the lower jaw fail to meet simultaneously.

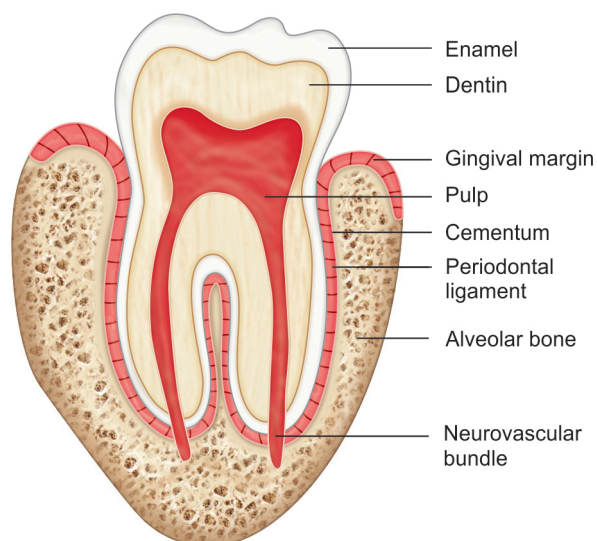


Fig. 45.1: Diagrammatic representation of the structure of the normal tooth.

Normally, the teeth of the upper jaw are in a position just inside those of the lower jaw. This contributes to a state when the outside mandibular cusps (incisal edges) meet the central portion of the opposing maxillary teeth. If this relation is reversed, the condition is termed **cross bite**.

In another situation, the posterior mandibular and opposing maxillary teeth make good contact with each other. However, the anterior teeth of the two jaws are still apart. This is termed **open bite**. In yet another situation, the posterior teeth of the two jaws are together, but the mandibular anterior teeth occlude inside the maxillary anterior teeth in an overclosed position. This situation is termed **closed bite**.

Ideally, moderate spacing of primary incisors is desirable so that the subsequent teeth are adequately aligned. If there is lack of spacing between primary incisors, or these show overlap, **dental crowding** involving the permanent incisors at 7 or 8 years of age is likely to result. Thumb-sucking when vigorous may cause an **open bite**. If it continues beyond the time of eruption of permanent teeth, maxillary arch and the incisor teeth may well be distorted. Malocclusion requires orthodontic treatment, including bracing.

DENTAL CARIES

The term refers to a progressive dental decay comprising decalcification of the enamel and dentin, resulting in formation of a cavity that, if left untreated, spreads into the pulp and gives way to inflammation and abscess.

Etiopathogenesis

Three cardinal factors and the interrelationship between them play major role in causation of dental caries. These factors are:

1. Tooth surface
2. Dietary carbohydrates and sugars, primarily sucrose
3. Specific oral bacteria.

The decay process starts following demineralization of the outer tooth surface (enamel) from the effect of organic acids produced by the bacterial fermentation of dietary carbohydrates. Incipient lesions first make their appearance as opaque white spots. With progress loss of dentine, cavitation occurs. The cavity, if not treated, spreads into the pulp. This may cause inflammation and an abscess. At this stage, it becomes very difficult to save the tooth.

The cariogenic microorganisms, grouped as *Streptococcus mutants*, are believed to initiate most dental caries of enamel surfaces. The *Lactobacillus* and other oral bacteria invade the underlying dentin after the

enamel surface has cavitated, causing further destruction through a mixed bacterial infection. A noteworthy point is that, rather than the quantity of carbohydrates consumed, frequency and the longevity of retention in the oral cavity is more important for the cariogenic effect.

High-risk conditions for dental caries include faulty salivary gland function (drugs that cause xerostomia, Sjögren syndrome, Mikulicz disease, chronic graft-versus-host disease), gastroesophageal reflux (GER), bulimia, rumination, mental retardation, Prader-Willi syndrome, dystrophic epidermolysis bullosa, sleeping with the feeding bottle, very high frequency breastfeeding, use of dummy or pacifiers which have honey or some other sweetening agents, etc.

Clinical Features

Early dental caries are, as a rule asymptomatic. These begin in the pits and fissures of biting surfaces of the molars. These are detected by the dentist by probing. The pit and fissure caries of long duration can easily be detected as extensive cavities.

The second most common site of caries is contact surfaces between teeth. It is usually detected by intraoral X-rays. Caries involving necks of the teeth are uncommon in children, except those with nursing bottle caries (NBC), also termed **baby bottle tooth decay (BBTD)**. Significant toothache occurs when the dental caries spread to involve the pulp and contagious tissues. Pulpitis may be complicated by dental or periapical abscess which is very painful (Fig. 45.2). Sepsis may complicate the picture.

Treatment

Pain and inflammation with caries involving only the dentoalveolar unit needs analgesic (paracetamol or a non-steroidal anti-inflammatory drugs {NSAID}) together with local measures like extraction, pulpectomy, etc. minus antibiotics. Pain and inflammation from caries involving



Fig. 45.2: Nursing bottle caries (NBC). Involvement of the neck of the tooth is the characteristic feature of NBC, also termed—"baby bottle tooth decay"—(BBTD).

structures outside the dentoalveolar unit, antibiotics must routinely be administered. Parenteral antibiotics are indicated in the following situations:

- Infection involving vital area such as submandibular space, facial triangle, periorbital space.
- Oral antibiotics are not effective.
- Susceptibility to endocarditis.
- Immunocompromised status.

Prevention

- **Fluoride:** It protects the tooth enamel from decay. Fluoridation of water supply dietary, fluoride supplements and topical application of fluoride agents either professionally or by the child (fluoride toothpaste) are beneficial in prevention of caries.
- **Dietary modification:** Reducing the frequency of carbohydrate ingestion, avoiding oral retaining of carbohydrate containing food products (chewing gum containing sucrose) for a long time and discouraging bottlefeeding and use of dummies (pacifiers) prevent dental caries.
- **Oral hygiene:** Correct tooth brushing and flossing (even though it needs greater parental involvement) is vital in caries prevention.
- **Dental sealants and plastics:** Development pits and fissures on occlusal surfaces of teeth should be sealed by the application of photocured biphenylglycidyl dimethacrylate (Bis GMA) resin film for preventing caries.
- **Identification of high-risk children:** Appropriate preventive measure can safeguard against caries in them.

FLUOROSIS

The caries preventive role of fluoride is well established. Nevertheless, high serum levels of fluoride (usually from drinking water or toothpaste having very high content of fluoride) may cause high serum levels of fluoride. The result is developmental anomalies of enamel in the form of white flecking or linear opacity of the enamel. This condition is termed **fluorosis**. The disease is rampant in several parts of India where drinking water contains over 2 parts/million of fluoride. Extradental manifestations of fluorosis such as involvement of the vertebral column and spinal cord with paraplegia, take decades to manifest.

GUIDELINES FOR PREVENTION OF DENTAL DISEASE

Dental or Oral Hygiene

Good orodental hygiene, involving cleanliness after each and every meal and correct brushing, ensures removal of the food particles that may form focal points for tooth decay, contributes to healthy teeth. Application of the fissure **sealants** is found highly effective in safe-guarding against dental caries.

Diet

Added sugars in the form of sweet drinks, biscuits, cakes, candies, sweets, etc. especially when consumed

816 frequently are the main culprit for dental caries. The practice of consuming these substances frequently must be cut down and proper cleansing of the teeth of their intake ensured.

Fluoride and Fluoridation

In areas where fluoride content of water is inadequate (under 1 ppm or 1 mg/L) and fluoridation of water is yet not done, the following measures may be adopted:

- Self application through use of fluoride toothpaste, making sure that young children are not exposed to excessive consumption.
- Topical application of fluoride solution or gel by the dentist.
- Fluoride tablets or drops given from an early age so that both temporary and permanent teeth are protected.
- Fluoridized salt.

Regular Dental Check-ups

Regular and frequent dental check-ups, which may involve professional cleaning, removal of plaques and polishing contributes to prevention of dental disease.

CLEFT LIP AND PALATE

Cleft lip (Figs 45.3 and 45.4A to C) may be unilateral or bilateral, the extent varying from a notch in the vermillion border to a large cleft reaching the floor of the nose. Accompanying anomalies include cleft palate, and supernumerary, deformed or absent teeth.

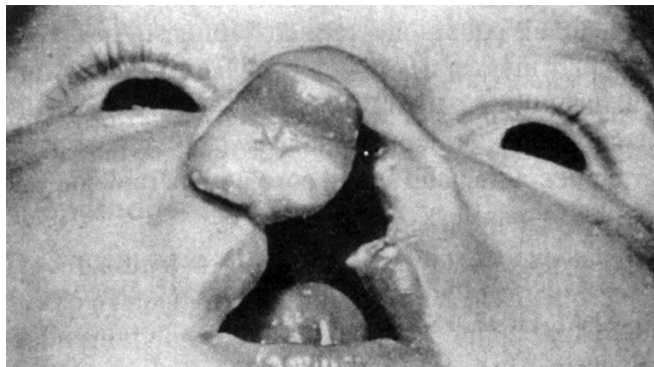


Fig. 45.3: Cleft lip (bilateral) extending into both nostrils.

Cleft palate, when occurring in isolation, is in the midline. It involves only the uvula or reaches the incisive foramen through soft palate. When occurring in association with cleft lip, it involves the soft palate and exposes the nasal cavity on one or both sides depending upon whether the defect is unilateral or bilateral.

Complications include aspiration, recurrent otitis media, dental caries, dental malocclusion and speech defects. Treatment is surgical closure at 1–2 months for cleft lip and 6 months to 5 years for cleft palate. Pending surgical correction, the baby should be fed in an upright position, employing softened nipples with somewhat bigger holes, so that aspiration does not occur.



A



B



C

Figs 45.4A to C: (A) Cleft lip (unilateral) extending into the right nostril; (B) Bilateral cleft lip with cleft palate. The child also had umbilical hernia (not include in the picture); (C) Bilateral cleft lip and cleft palate.

Multiple Choice Questions

1. All the following observation about dentition are true, except:
 - A. Initiation of primary dentition occurs around seventh week of gestation
 - B. Initiation of permanent teeth occurs around fifteenth week of gestation
 - C. Canine are the first permanent teeth to appear followed by incisors and molars
 - D. Once matrix is formed, another two months are required for calcification

contd...

2. Major problems occurring as a result of dental malocclusions are each of the following, except:
 - A. Cosmetic disfigurement
 - B. Erroneous mastication
 - C. Speech problems
 - D. Loss of teeth
3. What is not correct about dental caries?
 - A. Streptococcus mutants is a group of cariogenic microorganisms
 - B. Quantity of carbohydrates consumed is more important in causation of caries than the frequency and longevity of their retention in the mouth
 - C. Early dental caries are asymptomatic
 - D. Nursing bottle caries involve the neck of the tooth, a situation that is uncommon in children as such
4. Spot the wrong statement about fluorosis:
 - A. Characteristic dental lesion is a white flocking or bilinear opacity of the enamel
 - B. Cause is always drinking water with very high content of fluoride
 - C. It is rare in India
 - D. Extradental manifestations include involvement of vertebral column and spinal cord
5. Spot the wrong observation:
 - A. Caries makes a beginning after the demineralization of the enamel
 - B. The term malocclusion implies malposition and imperfect contact between mandibular and maxillary teeth
 - C. Cleft palate should undergo surgical closure after 6 months of age
 - D. Periapical abscess is always painless

Answers

1. C 2. C 3. B 4. C 5. D

Clinical Problem-solving

Review 1

A 9-year-old, who had been indulging in chronic and vigorous thumb-sucking and still indulges in it at times, presents with some disfigurement of the face and difficulty in mastication overlap and overcrowding of incisors.

1. What according to you should be the diagnosis?
2. What is it?
3. What is the way out?

Review 2

A 6-day-old neonate presents with unilateral cleft lip extending into the nostril so that nasal cavity is exposed. Examination shows that the infant also has cleft palate.

1. What are likely complications in this child with both cleft lip and cleft palate?
2. When should surgery be done for cleft lip?
3. What is the recommendation for corrective surgery on cleft palate?

Answers**Review 1**

1. Dental malocclusion secondary to vigorous and chronic thumb-sucking.
2. Malocclusion is malposition and imperfect contact of the mandibular teeth with maxillary teeth, causing cosmetic disfigurement, erroneous mastication and later, even loss of teeth.
3. Orthodontic treatment, including bracing.

Review 2

1. Complications of cleft lip and cleft palate include aspiration, recurrent otitis media, dental caries, dental malocclusion and speech defects.
2. Surgical closure for cleft lip should be at 1–2 months of age.
3. In case of cleft palate, surgical closure recommended late, i.e. after 6 months but certainly by 5 years of age.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

1. Gupte S. Feeding bottle caries: Risk factors. In: *Scientific Abstracts, 8th Asian Congress of Pediatrics* New Delhi, 1994. Abs No FD19/22:141.
2. Singh G, Joshi JL. Dental problems of the handicapped child. In: Gupte S (ed): *Recent Advances in Pediatrics-7*. New Delhi: Jaypee 1997:265–280.

BOOKS/MONOGRAPHS

1. Sidney BF. *Clinical Pedodontics*. Philadelphia: Saunders 1991.
2. Waterhouse E. *Pediatric Dentistry*, 4th edition London: Smith and Smith 2013.

GASTROINTESTINAL PROBLEMS**Congenital Hypertrophic Pyloric Stenosis**

This classical and common syndrome of obstructing pyloric circular muscular hypertrophy was initially considered to be developmental in origin, but now is thought to be acquired. There is some evidence of genetic predisposition and variability among different races. This disorder is certainly more common in western world as compared to India. The incidence is significantly higher in the first male babies.

Clinical Features

The typical presentation is with onset of non-bilious vomiting starting anytime between 1 week and 8 weeks of age and which progressively becomes forceful and projectile. The peak age of presentation is between 3 weeks and 5 weeks, though it may occur at birth and has been reported on prenatal ultrasonogram also. In general premature infants present 1–2 weeks later as compared to term infants. The vomiting typically occurs within 30 minutes of feeding and may contain coffee grounds also as a result of gastritis or esophagitis. Other features are constant hunger and failure to thrive (FTT).

Occasionally, greenish stools (starvation diarrhea), gastric hemorrhage or jaundice may be present. Dehydration, electrolyte imbalance—especially metabolic alkalosis, hypokalemia and hyponatremia—and tetanic spasms may complicate the picture.

The important clinical findings include epigastric fullness, gastric waves moving from left to right and a palpable lump (olive-shaped) in the right upper quadrant. The palpation of lump requires diligence and clinical skill. The use of a pacifier or a small feed, covering the infant and examining while in mother's lap are all helpful maneuvers. Failure to palpate pylorus necessitates further work-up to rule out severe gastroesophageal reflux (GER), antropylic webs, pyloric atresia and duplication anomalies.

Diagnosis

Clinical impression is confirmed by ultrasound and, if still in doubt, by a barium meal study.

- Ultrasonogram—pyloric channel longer than 16 mm, pyloric muscle thickness more than 4 mm and pyloric diameter more than 14 mm are considered to be diagnostic.
- Barium study—the stomach is markedly distended with abnormal retention of barium, and there is increased

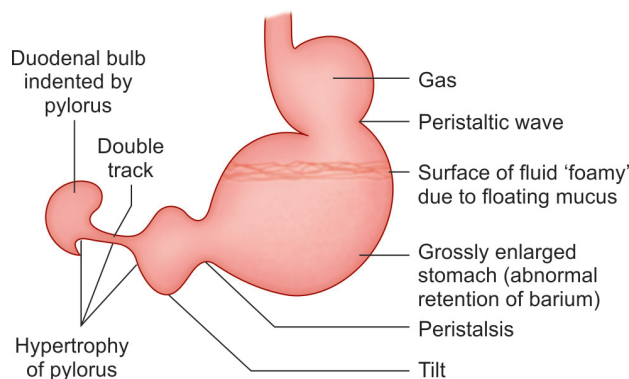


Fig. 46.1: Congenital hypertrophic pyloric stenosis. Diagrammatic representation of the radiologic appearance of congenital hypertrophic pyloric stenosis. At times, classical X-ray signs may not be demonstrable.

intensity of peristaltic waves and gross narrowing and elongation of pylorus with indentation of antral outline by hypertrophied pyloric muscle (Fig. 46.1).

Treatment

The treatment of choice is surgical division of hypertrophied muscle bundles of pylorus (Ramstedt pyloromyotomy). But before resorting to surgery, infant should be rehydrated and all the metabolic corrections should be done. The oral feedings should be discontinued and adequate sodium, chloride and potassium replacement should be given. As pyloric obstruction is partial, most infants will be able to tolerate their gastric secretions and a nasogastric tube is not routinely required.

Atropine-like drugs act by relaxing the circular muscles and recently there has been an interest in this type of management. But due to disadvantages of prolonged hospitalization, incomplete response and risk of atropine-related cardiac side effects coupled with uniformly good results of surgery, medical management of pyloric hypertrophy is not in vogue.

Hiatal Hernia**(Partial Thoracic Stomach)**

In the most common type of hiatal hernia in infants, cardiac end of stomach slides high up above the diaphragm and then back into the abdomen. Manifestations include regurgitation or vomiting (often projectile), FTT and anemia. Aspiration may cause pneumonia. Differential diagnosis is from pyloric stenosis and esophageal reflux resulting from brain damage and gross scoliosis. Indications for surgical repair are:

- Persistent vomiting
- Esophagitis
- Frequent aspiration
- Impending stricture.

Esophageal Atresia and Tracheoesophageal Fistula

Esophageal atresia (EA) and tracheoesophageal fistula (TEF) group of disorders (Fig. 46.2) comprise of anomalies ranging from classical proximal EA with distal TEF (85%) to just a H-type communication between esophagus and trachea (4%). The in-between shades include pure EA without TEF (8%), EA with both proximal and distal TEF (1.4%) and EA with only proximal TEF (<1%). Associated common anomalies are congenital heart disease 20–40%, ventricular septal defect (VSD), tetralogy of fallot (TOF), patent ductus arteriosus (PDA), atrial septal defect (ASD) and pulmonary stenosis (PS), genitourinary anomalies (20–25%, hypospadias, undescended testes, hydronephrosis) and gastrointestinal (20%, anorectal malformation, bowel atresias and malrotation) and skeletal defects (15%, vertebral defects, accessory ribs and sacral defects). The incidence of polyhydramnios in the mothers of such infant is high.

Clinical Features

The findings include excessive salivation (blowing bubbles), coughing, gagging and even choking, respiratory distress and cyanosis on the very first feed. Aspiration pneumonia may occur. Careful attention must be paid to a thorough examination of such baby to rule out associated anomalies.

Diagnosis

Choking, cyanosis and regurgitation after the first feed, more so in a baby born to a mother suffering from polyhydramnios, must arouse a strong suspicion.

On suspecting the condition, oral suction should be done to clear the pooled oral secretions before an attempt to pass a catheter is done. Then a stiff radio-opaque catheter 8–10 French size (like a commonly available red rubber catheter) is passed into the upper esophagus till a hitch is felt and is secured. Chest and abdominal X-rays are taken in anteroposterior and lateral views. The distal extent of upper pouch can thus be evaluated. Presence

of gas in stomach indicates communication of the distal esophagus with the trachea. A note should be made of associated pneumonitis, any cardiac anomaly, skeletal defects and intestinal abnormalities. An echocardiogram and a renal ultrasonography is a part of the work-up of such a child.

If H-type TEF is suspected, a prone lateral view of chest with instillation of water-soluble contrast by a tube placed in the esophagus as it is withdrawn is recommended for demonstration of fistula. If the suspicion is strong and contrast study equivocal, bronchoscopy remains the gold standard for diagnosis.

Treatment

Early diagnosis, adequate preoperative preparation and surgical repair may prove life saving. The usual repair is primary end-to-end anastomosis with ligation of the fistula. If it is not possible to do anastomosis or the baby has moderate or severe pneumonitis, gastrostomy is performed. The repair of the esophageal pouch is done when the baby is clinically stable.

After surgery, the baby is given intravenous fluids for 48 hours. On third postoperative day, feeding through gastrostomy or transanastomotic tube is started. By 10th day, oral feeding may be begun provided the general condition of the baby is good and a contrast esophagogram reveals adequate healing.

Babies with H-type fistula require division of fistula by cervical approach with repair of both trachea and esophagus. Most babies with pure EA have a long gap, which is not amenable to anastomosis. Either a delayed primary repair or esophageal replacement is required for such babies. During follow-up an eye is kept, as these babies are prone to develop anastomotic strictures. Evaluation is done by barium studies and then esophageal dilatations may be required.

Congenital Diaphragmatic Hernia

Etiopathogenesis

This condition is characterized by herniation of abdominal contents into thoracic cavity as a result of a developmental defect in the diaphragm (usually through the posterolateral foramen of Bochdalek on left side), pulmonary hypoplasia and malrotation of gut. Associated anomalies include EA, omphalocele, central nervous system (CNS) lesions, cardiovascular lesions and syndromes as trisomy 21, trisomy 13, trisomy 18.

Clinical Features

In the present era, a reliable diagnosis can often be made by an antenatal ultrasonogram performed at any time beyond 14 weeks as routine or later for evaluation of polyhydramnios. All such mothers should be referred to higher tertiary care centers for immediate neonatal care and surgery.

Eighty to ninety percent of the affected infants have neonatal respiratory decompensation within the first hour of life with tachypnea, retractions, cyanosis and gasping. Clinically, these neonates have asymmetric funnel chest

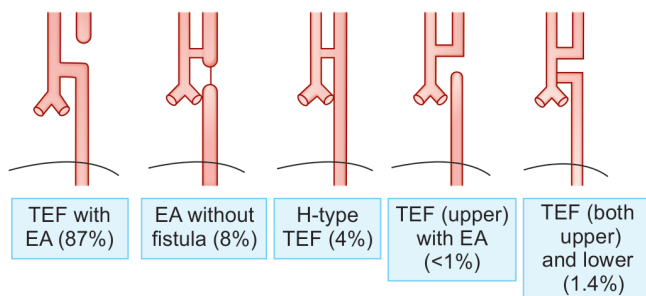


Fig. 46.2: Tracheoesophageal fistula and esophageal atresia.

Abbreviations: TEF, tracheoesophageal fistula; EA, esophageal atresia.

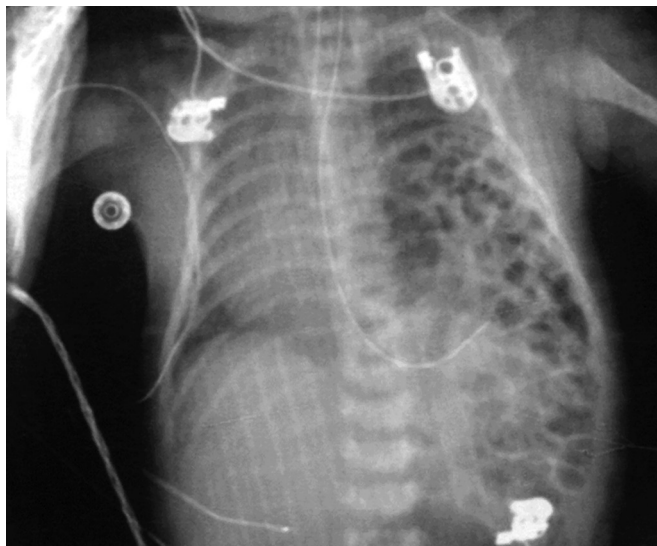


Fig. 46.3: Congenital diaphragmatic hernia (CDH). Note the multiple loops of bowel and a nasogastric tube coursing into the chest cavity with pushing of the heart to the opposite side.

with shift of the mediastinum, absent breath sounds and presence of peristaltic sounds on the affected side. Heart sounds are displaced and abdomen is scaphoid. Ten to twenty percent of children who present later do so with recurrent chest infections, abdominal pain or features suggestive of gastric volvulus.

Diagnosis

A plain X-ray of abdomen and chest in a suspected case shows intestinal loops in the chest cavity, a finding diagnostic of congenital diaphragmatic hernia (CDH) (Fig. 46.3). It is appropriate to do blood gas analysis to assess the extent of hypoxia and acidosis.

Treatment

After confirmation of diagnosis, all efforts are made to stabilize the cardiorespiratory system. As the respiratory distress in an infant with CDH results from interplay of two factors—(i) uncorrectable pulmonary hypoplasia and (ii) potentially controllable pulmonary hypertension, all efforts are made to decrease the pulmonary arterial pressures to decrease the right to left shunting.

A nasogastric tube is placed and a rectal syringing given to deflate the stomach and colon respectively. Ventilation by bag and mask is contraindicated and if required an endotracheal tube is placed. The infant is sedated and metabolic acidosis and hypoxia is corrected.

Congenital diaphragmatic hernia is no longer considered a surgical emergency; instead it is a physiological emergency to control the hypoxia by adequate preoperative stabilization. Once stable the child is taken up for laparotomy and reduction of viscera with repair of the diaphragm. Good results can be expected if the pulmonary hypoplasia is not very severe.

Duodenal and Other Intestinal Atresias

Partial or complete occlusion of the intestinal lumen may occur congenitally in any part of the intestine commonly

in duodenum (especially in Down's syndrome) followed by ileum, jejunum and colon. These children present with bilious vomiting and abdominal distension, which starts on day 1 of life. In general, lower the site of atresia more the abdominal distension and later the onset of vomiting (distension is not seen in duodenal obstruction due to proximal obstruction). Plain abdomen X-ray film shows **double bubble** sign in duodenal atresia. In jejunal atresias, three bubbles may be seen—**triple bubble sign** while in lower more air-fluid levels are seen.

Adequate hydration is ensured and the child is taken up for surgery. The procedure entails excision of the atretic segment and end-to-end anastomosis. Postoperatively resumption of bowel function is often delayed and these children require nutritional support in the form of total parenteral nutrition (TPN).

Intestinal Malrotation

In the intrauterine life, the embryologic midgut undergoes a counterclockwise rotation by 27° as it returns into the developing peritoneal cavity. As a result of this duodenojejunal flexure crosses over and lies to the left of spine and colon crosses over the small bowel mesentery and cecum assumes a position in the right lower quadrant. The term **malrotation** refers to incomplete rotation of the gut during intrauterine life so that cecum comes to lie below pylorus, root of mesentery becomes very narrow, ascending and transverse colon becomes mobile and vulnerable to twisting in a clockwise direction. This anatomical position predisposes to twisting to whole of the midgut on its narrow base—midgut volvulus which is an extreme surgical emergency as practically the whole of the small bowel may be lost. The other cause of obstruction in this scenario is due to Ladd's bands which course from abnormally located cecum across the second and third part of duodenum and cause external compression on duodenum.

Manifestations include:

- **Acute midgut volvulus:** Sudden onset bilious vomiting, rectal bleeding, abdominal distention and feeble or absent bowel sounds and shock. Most of these patients present in the 1st month of life.
- **Chronic midgut volvulus:** Recurrent abdominal pain and chronic malabsorption are the manifestations.
- **Duodenal obstruction:** It may occur secondary to Ladd's bands leading to acute upper gastrointestinal (GI) obstruction. More common in neonates and infants, the clinical picture includes recurrent forceful bilious vomitings without abdominal distension.

Diagnosis is from a plain abdominal film showing a large stomach bubble with few distal gas shadows. Barium meal studies show that the duodenojejunal junction lies over or to the right of spine and cecum is higher up. The small bowel loops are predominantly on the left side of the abdominal cavity.

Ultrasound may show abnormal orientation of the superior mesenteric artery and veins establishing the

diagnosis. Treatment is exploratory laparotomy followed by lysis of the Ladd's bands and widening of the base of the mesentery. A delay in surgery may result in bowel compromise and gangrene.

Intussusception

The disorder is characterized by telescoping of one of the portions of the intestine into a more distal portion, leading to impairment of the blood supply and necrosis of the involved segment. Of the three forms (ileocolic, ileoileal and colocolic), ileocolic is the most common. It is the most frequent cause of intestinal obstruction during the first 2 years of life.

Etiologic Considerations

The most common form is idiopathic and occurs classically between 4 months and 7 months of age. A pathologic lead point may be found in only 2–8% of the cases, especially after 2 years of age. The predisposing factors include Henoch-Schönlein purpura, Meckel's diverticulum, parasites, constipation, inspissated fecal matter in cystic fibrosis, foreign body, lymphoma and infection with rotavirus or adenovirus.

Clinical Features

These include episodic abdominal pain, vomiting and rectal passage of bloody mucus. Fever and prostration are usually appear 24 hours after the onset of intussusception and signify transmural migration across congested serosa. A sausage-shaped lump may be palpable in the upper abdomen in early stages. Rectal examination may show a cervix-like mass and blood on the examining finger (Fig. 46.4).

Diagnosis

- **Plain X-ray abdomen** may reveal absence of bowel gas in the right lower quadrant and dilated loops of small bowel.

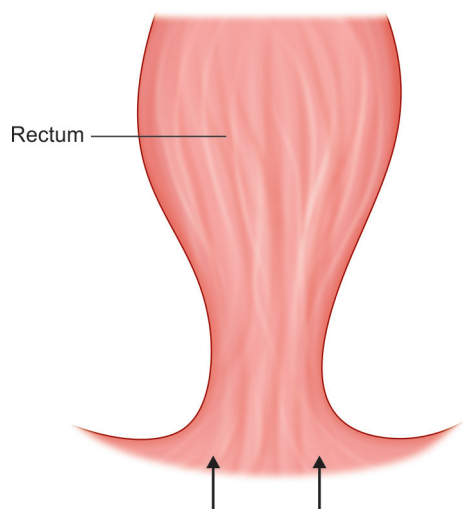


Fig. 46.4: Intussusception. Note that finger can be inserted into the rectum past the intussusceptum.

- **Ultrasound** will show a target sign in upper abdomen or in left iliac fossa due to presence of intussusceptum within the bowel.
- **Barium enema** may show the intussusception as an inverted cap or a claw sign may be seen. There is an obstruction to the retrograde progression of barium into ascending colon and cecum. In the area of intussusception, there may be a ceiling-spring appearance to the column of barium.

Treatment

Conservative **hydrostatic reduction** gives good results in a large majority of the cases, provided that there is no evidence of strangulation, perforation or severe toxicity. It is performed by insertion of an unlubricated balloon catheter into the rectum. The balloon is then inflated and pulled down against the levator ani muscles. Thereafter, buttocks are strapped together. From a height of 90 cm, barium is allowed to flow into the rectum. Under fluoroscopy, the progress of barium is noticed. Total reduction is judged from:

- Free flow of barium into the cecum and reflux into the terminal ileum
- Disappearance of the lump
- Passage of flatus and/or stools per rectum
- Improvement in the patient's general condition
- Passage of charcoal, placed in child's stomach by the nasogastric tube, per rectum.

Surgical reduction is indicated in patients who are unfit for hydrostatic reduction or who fail to respond to hydrostatic reduction after two attempts.

Prognosis

Left unreduced, intussusception is invariably fatal. Spontaneous reduction with recurrent episodes is known in older children.

Hirschsprung's Disease

(Congenital Megacolon)

This disorder results from absence of parasympathetic ganglion cells in both Meissner and Auerbach's plexuses at rectosigmoid segment with or without involvement of some additional part of the distal large bowel. The patients with Down's syndrome show far higher incidence. In males, it is about five times more frequent.

Clinical Features

Constipation (persistent, not responding to various measures), abdominal distention, vomiting and growth failure may begin soon after birth. Often, constipation may alternate with paradoxical diarrhea. The patient is generally grossly malnourished with multiple nutritional deficiencies. The loops of bowel may be palpable.

On rectal examination, no stool is found. But, as soon as the finger is removed, the child may pass lots of flatus and watery stool. This observation is in sharp contrast with the loaded rectum of psychogenic megacolon.

822 Investigations

A strong clinical suspicion of congenital megacolon is an indication for the following investigations:

- **X-rays:** An upright plain film shows remarkably distended bowel with gas and stools. At times, air-fluid levels and air in the wall of the gut may be present.
- **Barium enema:** In a newborn, barium enema may show prolonged retention of barium for over 24 hours. In later age group, it shows that the involved segment is constricted and has irregular outline. The colon proximal to this spastic segment is grossly distended. In between the distended and the constricted segment there is so called **transition zone** which is considered diagnostic for Hirschsprung's disease. In a less classical case, the only finding may be rectosigmoid inversion, i.e. sigmoid has a larger diameter than the rectum.
- **Rectal biopsy:** This is the gold standard for making the diagnosis. The best site for obtaining rectal biopsy in such a child is about 5 cm above mucocutaneous junction. Absence of ganglion cells in the plexuses confirms the diagnosis.

Treatment

Medical treatment with stool softeners and repeated enemas with isotonic saline is recommended only while waiting for surgery. During this period attempts should be made to maintain fluid and electrolyte balance and to build up the nutritional status. Antibiotics are indicated in the presence of enterocolitis, which is quite common and a continued threat to life in this disorder.

The treatment of choice is surgery, involving resection of the involved (aganglionic) segment and end-to-end anastomosis to establish continuity between the rectum and the proximal segment. Various types of pull through operations namely Soave's, Duhamels and Swenson's pull through have been devised, but all of them essentially achieve the same above said goal. It is advisable to perform colostomy prior to this operation, more so in poor-risk cases. The best time to perform the main operation is at or soon after the infant has attained the age of 6 months.

Prognosis

Unoperated cases are always at risk of enterocolitis, obstruction or perforation, which may prove fatal. Following surgery, outlook for life is excellent. Over 90% of them recover completely with normal growth and normal bowel habit. Occasionally, fecal incontinence due to damage caused during surgery may become troublesome.

Meconium Plug Syndrome

The term refers to impaction of a thick plug of meconium in the distal colon leading to manifestations of intestinal obstruction. It usually responds to a rectal wash, which brings out the obstructing meconium plug. It has a broad whitish head and a greenish meconium tail followed by a light-colored meconium. Some neonates may need another wash before proper defecation pattern develops.

Meconium Ileus

This condition occurs in neonates with cystic fibrosis. See Chapter 29 (Pediatric Gastroenterology). The viscid mucus tends to choke the lumen of the intestine, causing manifestations of distal intestinal obstruction notably pellets of meconium are found in terminal ileum. At times, meconium may be palpable in the right lower quadrant of abdomen as a doughy and rubbery mass.

A plain abdominal X-ray reveals dilated intestine without fluid levels and a gastrografen enema highlights the microcolon. Treatment is surgery, provided that the enema has failed to relieve the obstruction by dissolving the inspissated mucus. Surgery involves either a tube enterostomy to facilitate the wash outs directly from the terminal ileum or creation of a double barrel or a Y stoma.

Meckel's Diverticulum

Abnormal persistence of embryologic vitellointestinal duct results in Meckel's diverticulum. It is seen in 2% of population, 2 feet (60 cm) from the ileocecal junction, is generally 2 inch (5 cm) long, containing heterotopic pancreatic tissue in 2% cases and is often symptomatic before 2 years of age.

Clinical Features

Presentation is with painless lower GI bleed or obstruction due to a band going up to umbilicus or perforation secondary to ulceration due to ectopic gastric mucosa. Some cases may present with right lower quadrant pain presumably due to inflammation of the diverticulum.

Diagnosis

Most important diagnostic tool is high index of suspicion. Confirmation of diagnosis is by a barium meal study or, better, a technetium-99m-labeled radionuclide scan.

Treatment

Treatment is surgical excision of the diverticulum-diverticulectomy.

Necrotizing Enterocolitis

This is the most common and most serious gastrointestinal condition encountered in the neonatal intensive care unit (NICU). It is discussed in details in Chapter 17 (Neonatology). Table 46.1 lists the indications of surgery in necrotizing enterocolitis (NEC).

Table 46.1: Indications of surgical intervention in NEC.

Definite indications	Probable indications
<ul style="list-style-type: none"> • A palpable abdominal lump • Pneumoperitoneum • Abdominal wall erythema • Positive abdominal tap (paracentesis) • X-ray abdomen • (Dilated loops, gasless with ascites) 	<ul style="list-style-type: none"> • Abdominal tenderness • Severe hemorrhage • Clinical deterioration • Platelets <100,000/mm³

Abbreviation: NEC, necrotizing enterocolitis

Appendicitis

This is the most common surgical emergency of childhood. It manifests initially with the classical triad of periumbilical pain followed by vomiting and fever. Later, pain shifts to right lower quadrant due to irritation of the adjacent peritoneum. Untreated cases go on to develop perforation peritonitis. The pain becomes generalized, fever and tachycardia increase and the abdomen becomes tender and distended. In a fortunate circumstance omentum seals off and localizes the peritonitis, and an abscess is formed in the right lower quadrant or pelvis.

A persistent direct tenderness over McBurney's point and rigidity of the overlying rectus muscle is highly suggestive of acute appendicitis. In doubtful cases, imaging studies like ultrasonogram or a non-contrast enhanced thin cut computed tomography (CT) scan may be helpful.

The appropriate treatment for acute appendicitis is surgical appendectomy within a few hours of diagnosis. In the event of a localized appendicular abscess, it should be drained by open or percutaneous technique and appendectomy performed in 4–6 weeks.

ANORECTAL PROBLEMS

Imperforate Anus and Other Anorectal Malformations

Imperforate anus with fistula may be of high, intermediate or low variety. In the high variety, the defect is situated above the levator ani funnel and the fistula opens into the urinary bladder (rectovesical fistula) at the level of the bladder neck in males and vagina (rectovaginal fistula) in females. In the intermediate variety, the defect lies below the levator ani funnel and is associated with fistula into the posterior urethra (rectourethral fistula). In the low variety, the defect is below the levator ani funnel and the fistulas open at the site of anus, perineal raphe or scrotal raphe in males and vestibule or vulva in females.

For determining the level of the defect, it is useful to perform a radiograph with the infant held upside down (suspended by legs). In this procedure, termed **invertogram**, air passes down the blind rectum and rises up in this position to demonstrate the level of rectal pouch. Treatment of low variety (primarily perineal fistulas) is a simple anoplasty without a protective colostomy. 2 weeks following operation anal dilatations are started and gradually increased to the size of a normal anus. Prognosis is excellent.

The currently recommended approach for high and intermediate varieties is a colostomy during the neonatal period followed by corrective surgical repair later in the first year of life per se, prognosis is good in imperforate anus without fistula with 80% subjects attaining good bowel control between 3 years and 4 years of age. Minimal soiling may continue in the rest.

Anal Fissure

(Fissure-in-ano)

Anal fissure is the most frequent cause of fresh rectal bleeding and usually follows a tear or small laceration of the mucocutaneous junction of the anus during passage of a hard fecal matter in a severely constipated child. A vicious cycle of constipation—painful defecation—stool retention—constipation sets in. A simple anal examination demonstrates the fissure. Treatment aims at softening stools by dietary correction and use of stool softeners so that the healing area is not stretched. Surgical intervention in the form of excision of the fissure, anal sphincterotomy or stretching of anus is in actuality not required.

Perianal Abscess and Fistula

Two types are known:

1. A **self-limiting benign form**, which occurs in infants with no particular predisposition and requires no treatment.
2. A **serious form** which occurs after the age of 2 years and has predisposing factors such as neutropenia, leukemia, diabetes mellitus, acquired immunodeficiency syndrome, Crohn's disease, peri or rectal surgery (imperforate anus, Hirschsprung's disease) or use of immunosuppressants.

Manifestations in the benign type include fever, rectal pain and perianal cellulitis. In the benign type, a pustule forms and the abscess is drained out. Occasionally, it may need drainage under local anesthesia. If a fistula has been formed, a fistulectomy is required.

In the serious type, cellulitis becomes more fulminant and spreads upward into the ischioanal fossa, leading to toxemia and even septicemia. In addition to aggressive treatment with broad-spectrum antibiotics, wide excision and drainage become mandatory. Fistulas in these cases are difficult to treat.

Pilonidal Sinus and Abscess

The term, **pilonidal sinus**, denotes a depression or dimple in the intergluteal cleft at the level of the coccyx in otherwise normal infants. Some of these children may develop pilonidal abscess, which may need incision and drainage followed by an en bloc resection of the tract.

ANOMALIES RELATED TO THE UMBILICUS

Vitellointestinal Fistula

This is persistence of the entire vitellointestinal tract duct. The infant presents with an umbilical sinus that keeps discharging either mucus or even stools. Probing shows a tract that leads down from the umbilicus and passage of tube into the tract causes exit of a greenish intestinal fluid. The fistula may be complicated by kinking or internal herniation. Treatment is surgery.

824 Umbilical Polyp

It is an intestinal mucosa lined patch in the umbilicus that presents with discharging umbilicus. Treatment is surgical excision.

Umbilical Hernia

Surgical intervention in umbilical hernia is required when it persists beyond 3–5 years or when it shows further increase in size after 1 year of age. A rare indication is when it gets strangulated. For details, See Chapter 17 (Neonatology) and Chapter 48 (Miscellaneous and Unclassified Issues).

Exomphalos (Omphalocele) and Gastroschisis

Exomphalos is characterized by herniation of the abdominal viscera through a wide-open umbilicus, the magnitude of herniation varying with the size of the umbilical patency. The exomphalos has a sac lined by a translucent membrane that merges with the skin. It may be seen as a component of Beckwith syndrome (exomphalos, macroglossia, gigantism). More than one-third of the cases have major cardiac anomaly warranting an echocardiogram.

Gastroschisis is characterized by herniation of the abdominal viscera through a defect in the abdominal wall, the umbilicus remaining well-formed without any opening. Unlike in exomphalos, there is no sac in gastroschisis. Intestinal atresia is associated in upto 20% of the cases, the most frequent association.

Surgical treatment aims at reduction of the abdominal viscera back to the abdominal cavity and closure of the abdominal wall. Due to exposure of the intestine, these infants are at risk of evaporative fluid losses and require aggressive fluid therapy and proper coverage of sac and viscera with sterile plastic bag till surgery. Other life-threatening issues are infection and hypothermia.

Post surgery babies often take time to resume bowel activity and in this regard TPN has improved the outcome in last two decades. Ventilation may be required for giant omphaloceles, which are managed with staged repair.

ANOMALIES OF THE HEPATOBILIARY SYSTEM

Extrahepatic Biliary Atresia (EHBA)

The obliterative disorder of extrahepatic bile ducts, an important cause of prolonged obstructive jaundice, usually manifests during neonatal period.

Etiopathogenesis

It is, by no means, a developmental defect. Three hypotheses have been put forward about its etiology. Firstly, it may well result from intrauterine viral infection which, when severe enough, causes inflammatory degeneration of the bile ducts and their replacement by fibrous tissue. Secondly, intrauterine ischemia of bile ducts has been incriminated as the cause of degeneration, disappearance and replacement with fibrous tissue of bile ducts. Thirdly, an unknown autoimmune reaction could

be responsible for damage of bile ducts. Currently, three anatomic types are recognized:

1. **Type I:** Atresia of common bile duct,
2. **Type II:** Atresia of common hepatic duct
3. **Type III:** Atresia at porta hepatis.

Type III is the most common type, accounting for over 85% of the cases and is also labeled as the uncorrectable variety. It must be appreciated that the obliterative process is of a progressive nature. Delay in corrective surgery beyond 3 months of age significantly reduces chances of finding patent ductules at porta hepatis. Liver biopsy at this stage may show intracellular and intracanalicular cholestasis, inflammatory cell infiltration, intestinal fibrosis, degeneration and proliferation of ducts and even giant cell formation. This picture is very much similar to that seen in neonatal hepatitis.

Clinical Features

The earliest manifestation is jaundice appearing round about the 7th day after birth (even days and weeks later). Jaundice, which is of obstructive type, is mild to begin with but progressively becomes severe. Stools are clay-colored (even white) and putty-like. Urine is heavily bile-stained. Skin in due course becomes bronze, olive green in color. Hepatosplenomegaly (Fig. 46.5) and vitamin deficiencies, especially hemorrhages due to vitamin K deficiency, may occur.

Diagnosis

Main differential diagnosis is from neonatal hepatitis See Chapter 25 (Fever Spectrum). However, at times, no single or battery of tests may conclusively differentiate the two. Such cases should have operative cholangiogram before 8 weeks of age to demonstrate the patency or obliteration of bile ducts at a specialized center.

Treatment

The surgical procedure of choice is Kasai hepatoporto-enterostomy. The basis of this procedure is that, although



Fig. 46.5: Extrahepatic biliary atresia. Besides hepatosplenomegaly, the infant had gross obstructive jaundice and hemorrhages.

extrahepatic bile ducts are fibrosed and obliterated, a good number of patent ductules converge at porta hepatis and when transected, discharge the pentup bile. In this operation, a loop of jejunum is anastomosed to the transected porta hepatis. In due course, ductal epithelium grows circumferentially and unites with the jejunal epithelium.

Prognosis

With early surgery, 40–50% long-term survival is reported. Most of the survivors may, however, show disturbed liver function, esophageal varices and hepatosplenomegaly. Recent advances include liver transplant if the Kasai's procedure fails to result in adequate drainage. Good results have been reported from the USA and Japan.

Choledochal Cysts

No longer considered rare, choledochal cysts are congenital dilatation of the common bile duct that may end up in progressive biliary obstruction and biliary cirrhosis.

Varieties

Five types of choledochal cysts are currently recognized:

1. **Type 1:** Saccular or fusiform dilatation of the extrahepatic biliary tree
2. **Type 2:** Diverticulum of the extrahepatic duct
3. **Type 3:** Choledochoceles
4. **Type 4:** Multiple cysts, intra or extrahepatic, or both.
5. **Type 5:** Single or multiple intra or extrahepatic cyst. The most common types are the cylindrical and spherical cysts. Around 90% are situated in the extrahepatic region.

Etiopathogenesis

The etiopathogenesis remains speculative. The following explanations have been put forward:

- Persistence of hepatic antrum from embryonal stage
- Unequal growth during the solid stage of development
- Congenital localized weakness of the duct wall
- Distal obstruction due to abnormal choledochopancreatic junction with a long common excretory duct and a wide angle.

The possible mechanisms involved in the development of these cysts are:

- Increased intraluminal pressure due to:
 - Abnormal choledochus sphincter inferior
 - Fibrosis of sphincter of Oddi
 - Post-inflammatory ductal stenosis
- Weakness of the duct wall due to:
 - Congenital cause
 - Pancreatic enzymes
 - Chemical substances (bile plus pancreatic juice).

Clinical Features

The disease affects females four times more than males. In the infantile variety that accounts for 75% of the cases, presentation is with cholestatic jaundice (acholuric stools, dark-colored urine), smooth hepatomegaly, and severe liver dysfunction. Rarely, gallbladder may be palpable as a lump. In the adult variety, the older child presents with classic triad

of abdominal pain, jaundice and abdominal lump. Evidence of acute cholangitis in the form of pyrexia, right upper quadrant tenderness, leukocytosis, etc. may be present.

Diagnosis

Ultrasound is the best diagnostic tool for detecting both the intra and extrahepatic choledochal cysts. This modality may identify such cysts even prenatally. A hepatobiliary iminodiacetic acid (HIDA) scan may also prove useful by delineating the cyst and provides some information about the liver function also.

Magnetic resonance cholangiopancreatography (MRCP) is very accurate and gives high resolution information about the exact ductal anatomy. Disadvantages are its cost and availability.

Treatment

Primary excision of the cyst and Roux-en-Y choledochojejunostomy is the treatment of choice. This procedure has uniformly good results. Postoperatively, rarely there is risk of suffering from complications such as anastomotic stricture, which leads to recurrent cholangitis.

Cholecystitis (Calculus Type)

For details, See Chapter 25 (Fever Spectrum).

GENITOURINARY PROBLEMS

Obstructive Uropathy

Congenital Ureteropelvic Junction Obstruction

This is the most frequent site of obstruction in the upper urinary tract and is the most common underlying disorder leading to a diagnosis of antenatally detected hydronephrosis. Most of the time obstruction is due to improperly developed musculature at ureteropelvic junction (UPJ). Other causes are from aberrant vessels (abnormal lower polar renal arteries crossing the UPJ), bands, kinks, valves, polyps, intrinsic anomalies or vesicoureteral reflux. It is bilateral in 20% cases. It can be diagnosed antenatally by ultrasonography at 20 weeks or postnatally by intravenous urogram (IVU), diuretic renal scan and voiding cystourethrography (VCU). Antenatal intervention is indicated in bilateral obstruction with equivocal function diagnosed early in intrauterine life. Indications of postnatal surgery are symptomatic obstruction, especially with compromised renal function and presence of caliectasis, decreasing function on follow-up nuclear scans or thinning of cortex on ultrasonography.

Posterior Urethral Valve

This is the most severe of the obstructive uropathies and can be diagnosed antenatally by ultrasonography. Anatomically, there is obstructing membrane of valve leaflets in the posterior urethra just distal to verumontanum. Manifestations result from the severe bladder outflow obstruction that accrues. Postnatally, manifestations include FTT, dehydration with dyselectrolytemia and acidosis, dribbling, straining to pass urine, urinary tract infection (UTI) and a persistently palpable urinary

826 bladder. Diagnosis is confirmed by ultrasonography and VCU. Surgical intervention is in the form of decompression of the bladder followed by transurethral ablation of the valves. Rarely, if the child does not respond favorably to this procedure or cystoscopy is not feasible, vesicostomy or even ureterostomy may be required.

Renal Stone

As a rule, renal stones are far less common in childhood than in adults. Incidence in boys is higher than in girls.

Etiology

The causes of urolithiasis in pediatric age group are:

- Metabolic:
 - Idiopathic calcium oxalate stones because of absorptive or renal hyperoxaluria, hyperuricosuria, hypocitraturia or most commonly hypercalciuria
 - Primary hyperoxaluria
 - Orotic aciduria
 - Enteric urolithiasis
 - Hypercalcemic states—hyperparathyroidism and immobilization.
- Renal disorders:
 - Cystinuria
 - Renal tubular acidosis
- Secondary:
 - Infection
 - Obstruction, commonly with PUJ obstruction
 - Structural or functional bladder anomalies
 - Post urinary diversion procedures
- Endemic bladder and renal stone disease.

Clinical Features

These include recurrent infections, renal colic (colicky abdominal or flank pain), hematuria and passage of gravel in urine. The signs and symptoms of the underlying disease may also be present. In an infant the features are often nonspecific.

Diagnosis

It is imperative to conduct a full metabolic work-up to rule out the above-mentioned causes otherwise a recurrence is likely. The work-up thus includes—renal function test, serum calcium and phosphorus, uric acid and hemogram. Fresh urine sediment should be examined under microscope for presence of crystals. It is equally important to measure the pH and to do the rest of the routine exam for RBCs and casts. 24-hour urine collection is done and excretion rates for calcium, phosphorus, uric acid, cystine and magnesium are estimated.

X-ray and ultrasonography of abdomen confirm the diagnosis of urolithiasis and rule out associated structural abnormalities. For planning of therapy, an intravenous pyelogram (IVP) may be required if some anatomical variation is expected.

Treatment

Treatment is directed at controlling the UTI if present, and assuring high fluid intake, which may reduce the

concentration of precipitate crystalloids and per se dissolve the calculus or push it out.

In case an underlying metabolic cause is discovered, proper preventive measures should be instituted accordingly. Options for removal include extracorporeal shock wave lithotripsy (ESWL), percutaneous techniques and open surgery.

Primary Bladder Stone Disease

The occurrence of bladder stone despite the absence of any obstructive uropathy, local predisposing cause in the bladder itself or infection among children tropical regions has aroused considerable interest. Besides India, it has been endemic in North Africa, Syria, Saudi Arabia, Iran, Burma, Pakistan, Thailand, Afghanistan and Indonesia. In India, the disease is common in Northeast states, Andhra Pradesh and Rajasthan followed by Delhi, Uttar Pradesh, Haryana, Punjab and Jammu and Kashmir. A large majority of the patients are under 10 years of age. Males are affected more often than females. The socioeconomic status of the families is usually poor.

Etiology

The exact etiology of primary bladder stone disease is not clear. The evidence condemning malnutrition is convincing though equivocal. Among the nutritional factors, borderline deficiency of phosphate appears to play a major role. High oxalate diet also contributes to this condition. It has been postulated that recurrent attacks of diarrhea may contribute to the problem by causing dehydration and concentrated urine. Likewise, recurrent febrile illnesses have also been incriminated in its etiology. Diet rich only in cereals without any milk or animal protein results in high urinary ammonium concentrations. Coupled with high urates, this leads to ammonium urate stones, the most common type in this scenario.

Clinical Features

Manifestations include dribbling of urine, painful micturition (pain over tip of penis is typical) and abdominal discomfort. Hematuria occurs occasionally. Superimposed UTI may complicate the clinical picture. In some children, genital handling, masturbation and rectal prolapse may also be noticed.

In a vast majority of the cases suffering from this disorder, there are no associated renal stones. Furthermore, recurrence rate following surgery is low. The stones are composed of mainly urates and oxalates.

Treatment

Surgical removal is the sole treatment of bladder stone.

Priapism

Rarely, children may suffer from nonerotic erection of penis for sustained periods which may be longer than 24–36 hours.

Etiology

The etiologic factors include leukemias, sickle-cell disease and perineal trauma.

Treatment

Spontaneous resolution may occur. Treatment of leukemia with chemotherapy and local irradiation of sickle cell disease with rapid hypertransfusion using packed red cells, of perineal trauma with surgical drainage of affected areas and creation of vascular shunt between corpus spongiosum and corpora cavernosa so as to produce detumescence leads to resolution of priapism. Sequelae include impotence, especially following post-traumatic priapism.

Tight External Urethral Meatus

(Meatal Stenosis)

A tight meatus with thin stream and, perhaps, some dysuria, on micturition may follow a healed meatal trauma, inflammation or ulcer, or an inappropriately timed circumcision. A generous meatotomy may be carried out.

Phimosis and Paraphimosis

Inability to retract the prepuce after the age of 3 years only should be regarded as **true phimosis**. As a rule, prepuce is unretractable at birth (**physiologic phimosis**), but in 90% instances it becomes retractable by the age of 3 years. By adolescent, only 1% have phimosis. Phimosis may be congenital or secondary to inflammatory condition(s) of the glans or prepuce.

Physiologic phimosis requires no intervention. Standard treatment for pathologic or true phimosis is surgical circumcision.

Alternatively, betamethasone cream may be applied to the narrowed preputial skin twice daily for 4 weeks. After 2 weeks, the foreskin becomes soft and elastic and is retracted gently and gradually in increments. In a vast majority, this treatment proves successful.

Paraphimosis means that once the prepuce (phimotic) is retracted behind coronal sulcus, it cannot be reduced. This causes venous stasis and edema with severe pain. Advanced cases need circumcision. In others, reduction can be attained by application of lubricants under cover of heavy sedation.

Hypospadias and Epispadias

The term, **hypospadias**, denotes abnormal placement of the external urethral meatus on the ventral aspect of the phallus. These cases need full evaluation for ambiguous sex and surgery.

Ambiguous Genitalia

For details, See Chapter 39 (Pediatric Endocrinology).

INGUINOSCROTAL PROBLEMS

Inguinal Hernia

It results from persistence of the patency of processus vaginalis accompanying the spermatic cord. An



Fig. 46.6: Inguinal hernia. Note the obvious swelling in the left inguinal region on crying. In view of the potential risk of strangulation, it must be operated as early as possible. Also note the umbilical polyp in this subject.

intermittent swelling in the inguinal or inguinoscrotal area appears, particularly on crying or straining (Fig. 46.6). It is reducible. Rolling of the cord between two fingers gives a feeling of crepitation. This is called **silk-glove sign**. It is helpful, but not really diagnostic of inguinal hernia.

Inguinal hernia requires operative treatment as early as possible in view of high incidence of obstruction and strangulation. The complications may manifest as red, irreducible swelling with abdominal distention, vomiting and constipation (obstructed or strangulated hernia). Incidence of complications is higher in preterm infants.

Hydrocele

The term, hydrocele, implies presence of peritoneal fluid within the tunica vaginalis.

- **Noncommunicating hydrocele** is quite common in newborns and infants. It disappears spontaneously by the age of 6 months. Right side is involved more frequently though bilateral involvement also occurs. The scrotal swelling is nontender and well transilluminated.
- **Communicating hydrocele** is characterized by rapid change in size in the subsequent months. There is a communication with the peritoneal cavity through the patent processus vaginalis. Hernia may accompany it. Surgical intervention is indicated only when hydrocele persists beyond 1 year of age. The operation involves ligation and division of patent processus vaginalis through a small inguinal incision.

Undescended Testes

(Cryptorchidism)

For details, See Chapter 39 (Pediatric Endocrinology). If cryptorchidism is left as such, diminished spermatogenesis may follow in adult life.

828 Epididymo-Orchitis

Inflammation of epididymis (epididymitis) testes (orchitis) or both (epididymo-orchitis) usually occurs following infection with mumps and coxsackie B viruses.

In case of mumps, orchitis usually follows parotitis within 8 days and subsides in 4–5 days. The testis becomes tender and swollen with red and edematous adjacent skin. One in three affected testes show atrophy in the long run. Nevertheless, infertility is infrequent. In case of coxsackie B viruses, orchitis (usually with epididymitis) follows recovery from illness characterized by fever and pleurodynia or meningitis.

Acute Scrotum

Acute scrotal swelling may result from epididymo-orchitis, torsion of testis or its appendages, testicular trauma or idiopathic scrotal edema. It is of paramount importance to differentiate between testicular torsion and the other causes, as torsion is a surgical emergency. Uncorrected torsion leads to testicular necrosis. Treatment is immediate surgical intervention, correcting the torsion and fixing the involved testis to the scrotum to safeguard against future torsion.

HEAD AND NECK PROBLEMS

Cleft Lip and Cleft Palate

For details, See Chapter 36 (Pediatric Dermatology).

Cystic Hygroma

(Lymphangioma)

These are massive, nontender, unilocular or multicystic tumors with semitransparent walls and thinning of the overlying skin. They make their appearance early in life—often at birth and occur in the head and neck region (Figs 46.7A and B) in 75% of the cases. With progression

in growth, hygromas may cause tracheal compression and respiratory distress. In some cases, associated enlargement of the tongue may occur.

Complications are bleeding and infection. Presence of erythema over the tumor is a sign of superimposed infection. Spontaneous regression does not occur. Treatment is surgical removal as early as possible. A large unilocular cyst may respond to intralesional sclerotherapy in the form of bleomycin, OK-432 (extracted from *Streptococcus*) or sodium tetradecyl sulfate.

Thyroglossal Cyst

It is a smooth rounded midline neck swelling which is connected by a tract to the base of the tongue, representing the persistence of the thyroglossal tract postnatally. It is likely to get repeatedly infected and burst. It should be differentiated from submental or pretracheal lymph nodes and ectopic thyroid gland, which, unlike the cyst, is always present at birth. Treatment is removal of the cyst along with the total tract by Sistrunk procedure. Excision of the body of the hyoid bone is a part and parcel of this procedure otherwise recurrence as likely.

Brachial Cyst

It presents late in childhood as a lateral fluctuating cystic swelling, full of a fluid with high cholesterol content, in the anterior triangle of the neck protruding from anterior border of sternocleidomastoid muscle. Treatment is excision.

Brachial Sinus and Fistula

Branchial sinus is a discharging sinus at the anterior border of sternocleidomastoid (the junction of its middle and lower thirds) and extends to external auditory canal above as branchial fistula. Treatment is careful excision as the tract passes in between the external and internal carotid arteries.



Figs 46.7A and B: Cystic hygromas. It is also called lymphangiomas, these tumors are capable of causing complications by their extension into the thorax and compression. Prognosis following early surgical resection is excellent.

Sternomastoid Tumor (Sternocleidomastoid Tumor)

The term refers to a hard, immobile, fusiform and well-circumscribed mass, around 2 cm in diameter, which may be felt in the middle of the sternomastoid muscle, usually 10–14 days after birth. There are no inflammatory signs, but the child has torticollis due to muscle shortening. In a large majority of cases, it slowly disappears by the age of about 6 months.

- The cause appears to be a birth trauma, usually from a difficult breech delivery.
- The condition must be differentiated from other causes of torticollis (Box 46.1).

Treatment consists of stretching the affected muscle to the overcorrected position by gentle manipulation several times daily. If response to conservative treatment continues to be discouraging by 6–12 months of age, surgical lengthening and division of the sternal portion of the muscle or from mastoid process at its origin followed by exercise program should be carried out. Else, the infant may develop asymmetry of the skull and face, cervicodorsal scoliosis and calcification in the involved muscle.

Box 46.1 Differential diagnosis of torticollis

- **Muscular:** Sternomastoid (sternocleidomastoid) tumor, neck muscle inflammation/trauma
- **Congenital anomalies:** Malformations of atlas, congenital cervical scoliosis, occipitocervical invagination
- **Rotatory fixation between C1 and C2** cervical adenitis, trauma, URI
- **Neurogenic:** Posterior fossa (cerebellar) or spinal cord tumor in older infants and children
- **Gastrointestinal:** GER, Sandifer syndrome.

Abbreviations: URI, upper respiratory infection; GER, gastroesophageal reflux.

MISCELLANEOUS PROBLEMS

Abscess

Abscess is a common pediatric surgery problem and signifies pus under pressure. Clinically, there is painful swelling with redness of overlying skin, fever and fluctuation on palpation. Abscess can occur virtually in any body part. Examples are breast abscess, abdominal wall abscess, psoas abscess, liver abscess, etc. Treatment entails surgical drainage and appropriate antibiotics. As the most common organisms are Gram-positive cocci (Staphylococcus and Streptococcus penicillin group of drugs which also cover the penicillin-resistant strains, i.e. cloxacillin) are effective. Abscess in the dangerous area of the face requires energetic and prompt therapy.

Multiple Choice Questions

1. Congenital hypertrophic pyloric stenosis usually presents:
 - A. Right at birth
 - B. In the second half of first month of life
 - C. Around 6 months of age
 - D. Around 1 year of age
2. An intestinal mucosa-lined patch in the umbilicus presenting with discharge from umbilicus is:
 - A. Omphalocele
 - B. Umbilical granuloma
 - C. Umbilical polyp
 - D. Vitello-intestinal fistula
3. Spot the wrong observation:
 - A. A choledochal cyst may end up as biliary cirrhosis
 - B. Stools are clay-colored in extrahepatic biliary atresia
 - C. Noncommunicating hydrocele is likely to persist beyond 1 year
 - D. A cystic hygroma usually appears in early infancy, often at birth
 - E. Phimosis at birth is usually physiologic, disappearing by 3 years of age in 90% cases
4. Each one of the following is a well-known cause of priapism, except:
 - A. Chronic myeloid leukemia
 - B. Sickle-cell disease
 - C. Perineal trauma
 - D. Hodgkin lymphoma
5. The best test for determining the level of defect in anorectal malformation is:
 - A. Ultrasonography of abdomen
 - B. Invertogram
 - C. X-ray of abdomen
 - D. Clinical workup

Answers

1. C 2. C 3. C 4. D 5. B

Clinical Problem-solving

Review 1

A newborn, immediately after birth, develops respiratory distress with cyanosis, chest retractions and gasping.

1. What is your diagnosis?
2. What are the likely associated abnormalities?
3. What findings are expected in chest X-ray?
4. How early is surgery recommended?

Review 2

A 3-month-old infant, weighing 4.8 kg, presents with small amount of blood in stool from time to time over several weeks. There is nothing suggestive of an intestinal infection and there is no abdominal discomfort. His hemoglobin is 8.5 g/dL.

1. What is the most likely diagnosis?
2. What is the pathophysiology of the condition?
3. How to confirm the diagnosis?
4. What is its treatment?

Answers

Review 1

1. Congenital diaphragmatic hernia.
2. Esophageal atresia, omphalocele, CNS lesions, CV lesions, and trisomy 21, 18 or 13.
3. CXR shows multiple air-containing lesions in left hemithorax with shift of the mediastinum to the right.
4. Rather than a surgical emergency, CDH is a physiological emergency. The first and foremost aim is to stabilize the cardiorespiratory system by decreasing the pulmonary arterial pressure. Laparotomy for reduction of viscera and repair of defect in the diaphragm follows stabilization.

Review 2

1. Meckel's diverticulum which results from persistence of embryologic vitellointestinal duct.
2. Bleeding in this condition occurs due to a band going up to umbilicus or perforation secondary to ulceration from ectopic gastric mucosa.
3. After the high index of suspicion, confirmation of diagnosis is by a barium meal study or yet better, a technetium-99m-labeled radionuclide scan.
4. Diverticulectomy is the treatment of choice.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

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CONGENITAL DEFICIENCY OF LONG BONES

Phocomelia is a reduction deformity (congenital amputation) in which there is gross reduction in the proximal part of the extremity so that distal part seems to be approaching the trunk. **Hemimelia** refers to absence of forearm and hand, or leg and foot (Fig. 47.1). **Amelia** means complete absence of limbs. Treatment in most cases revolves around amputation and orthotic rehabilitation.

CLUBFOOT

The most common type of congenital clubfoot is congenital talipes equinovarus (CTEV) in which foot is in plantar flexion and deviated medially. In the calcaneovalgus deformity, foot is dorsiflexed and deviated laterally. Association of clubfoot and spina bifida is well-known. Orthopedic treatment in the form of corrective manipulation with adhesive tapes, splints or casts and wedging is helpful, provided it is done as early as possible.

FLATFOOT

The term, **flatfoot**, denotes loss of medial longitudinal arch of the foot. Clinically, flatfoot is recognized when the arch touches the ground on weight bearing or is close to the ground. Until age 2–3 years, foot normally appears flat because of absence of the medial longitudinal arch.

Flatfoot may be congenital (calcaneovalgus deformity, hypermobility, rigidity with tarsal anomalies) or acquired (fracture of talus or calcaneus, tear of plantar ligaments,

muscle imbalance, postural, bad gait, faulty shoes). Treatment consists of conservative measures such as arch support, shoe modification and exercise. If this treatment fails, orthopedic intervention in the form of removal of calcaneus or, after age 10 years, arthrodesis.

RADIAL CLUB HAND

The hand is deviated laterally because of partial or total absence of radius. Absence of thumb, congenital heart defect and a bleeding diathesis are frequent accompaniments. Orthopedic treatment is centralization of ulna in relation to hand and reconstruction of thumb by pollicization of index finger.

TRIGGER THUMB

In this condition, the thumb cannot be straightened since it is locked in flexion because of a nodular swelling of the long flexor tendon at the base of the thumb. Treatment is surgical incision of the constricting mouth of the tendon sheath.

POLYDACTYLY

An extra finger/toe, usually close to the metacarpophalangeal joint of the little finger/5th toe or the thumb, may occur as an isolated trait or as a component of such syndromes as Laurence-Moon-Biedl syndrome, Carpenter syndrome, Meckel-Gruber syndrome and trisomy 13. It may be rudimentary or articulated. Orthopedic intervention is in the form of ligation or excision at birth or amputation at about 1 year of age.

SYNDACTYLY

Fusion of digits/toes varies from a cutaneous web to a synostosis and may occur as an isolated trait or as a component of certain syndromes like Apert syndrome, Carpenter syndrome, de Lange syndrome, Holt-Oram syndrome, oral-facial-digital syndrome, fetal hydantoin syndrome, Laurence-Moon-Biedl syndrome, Fanconi pancytopenia, trisomies 21, 13 and 18 and polysyndactyly syndrome.

CONGENITAL CONSTRICTION BANDS/RINGS

These are circumferential constrictions in the soft tissues, more frequently in legs and feet than arms and hands. Depending on magnitude of constriction, they cause obstruction in the circulatory and lymphatic channels, leading to localized edema. Associated foot deformities and superadded fractures of tibia and fibula are common. Treatment is excision of the constriction band.



Fig. 47.1: Hemimelia.

832 CONGENITAL PSEUDARTHROSIS OF THE TIBIA

In this condition, there is an aplasia of a portion (usually distal half) of the tibia, giving the impression of a non-healing fracture in the neonate. It may accompany neurofibromatosis. Orthopedic intervention is in the form of intramedullary nailing with bone grafting, vascularized fibular graft and electrical stimulation. Prognosis is poor.

DISLOCATION OF PATELLA

It may be congenital (ligamentous laxity on medial side of the joint, small lateral condyle of the femur, short quadriceps muscle) or posttraumatic. Two types are known—recurrent (occurring at intervals) and habitual (occurring whenever knee is flexed). Treatment is orthopedic correction.

KNOCK-KNEE (GENU VALGUM)

The term denotes medial angulation of knees because of outward deviation of the longitudinal axis of both tibia and femur. The concurrent finding is abnormally divergent ankles (intermalleolar distance >8 cm). Physiological knock-knee is common in toddlers, but it always disappears by age 7 years.

Treatment of a persistent knock-knee is stapling or osteotomy. The most common variety is idiopathic. It may also be secondary to bone softening (rickets, bone dysplasia, juvenile rheumatoid arthritis), post-traumatic (fractures), paralytic (post poliomyelitis residual paralysis, cerebral palsy), post-infective or neoplastic.

BOW LEG (GENU VARUM)

The term denotes lateral angulation of knee joints because of inward deviation of longitudinal axis of tibia and femur. As a result, knees are abnormally divergent bow-like whereas ankles are abnormally convergent.

Physiological bow leg, when the child begins to walk, is quite common. It resolves in due course. Other causes include rickets, postural, traumatic, developmental and endocrinal. A persistent deformity warrants orthopedic intervention in the form of corrective osteotomy.

CLEIDOCRANIAL DYSOSTOSIS

It is characterized by absence of the outer third of each clavicle so that the patient can make his shoulders meet in front, high-arched palate, absent paranasal sinuses, defective teething and poorly developed spinal bones. No treatment is indicated.

HEMIHYPERTROPHY

In this congenital disease, one side of the body is significantly larger than the other. The hypertrophy is usually of the whole one side, including face, tongue, teeth and genitalia.

Associated with hypertrophy of one side may be malformations like neurofibromatosis, hemangioma, nevi, polydactyly, cryptorchidism, hypospadias, tumors and calcification of adrenals and ichthyosis congenital hemidys-

plasia with ichthyosiform erythroderma and limb defects {CHILD} syndrome comprising of congenital hypertrophy, ichthyosis and limb defects). With gain in age, difference between the two sides often becomes less conspicuous.

SLIPPED CAPITAL FEMORAL EPIPHYSIS

This condition usually occurs in obese adolescents with delayed skeletal maturation or in tall and thin individuals with a recent growth spurt or in such endocrinal disorders as hypopituitarism, hypothyroidism or pseudohypoparathyroidism. An endocrinal origin is suspected. Four clear-cut groups are recognized—(1) pre-slip, (2) acute slipped, (3) capital femoral epiphysis (SCFE), (4) acute on chronic SCFE.

Manifestations include a painful limp and pain in the anterior aspect of thigh with radiation to the knee. External rotation of the hips on flexion is a pathognomonic sign. Radiographs (anteroposterior and lateral/frog leg view) are diagnostic. Orthopedic treatment is *in situ*. Complications are osteonecrosis and chondrolysis.

DEVELOPMENTAL DYSPLASIA OF THE HIP

Developmental dysplasia of the hip is also termed **congenital dislocation of the hip**; the global incidence of this condition varies from 0.7 to 15.5/1,000 live births. It is rather uncommon in India.

Etiology

In breech presentation and other difficult deliveries, the head of the infant's femur may get dislocated upward and backward. Its constant pressure over the dorsal aspect of the ileum may cause development of a false acetabulum. The defect occurs more frequently in females and is often hereditary.

Clinical Features

Every newborn must have an examination of the hips to rule out this disorder (Fig. 47.2). Asymmetry of the thigh, gluteal and knee creases, inability to abduct the hip fully, shortness of the affected leg, reduced spontaneous movements and a bulge of the femoral head must arouse suspicion. A good screening test (Ortolani sign) consists in abducting the hip passively. A clicking sound is heard from the hip at the end of the maneuver. It results from the jerking of the subluxated head as it reduces back into the acetabulum.

The **Barlow test** is the most important maneuver and consists in stabilizing the pelvis with one hand. Then, the opposite hip is adducted and a posterior force is applied. When the hip is dislocatable, it is readily appreciated.

Diagnosis

It is confirmed by X-ray and/or ultrasound of the hip. Differential diagnosis in older children is from dislocation of hip seen in hypothyroidism, cerebral palsy and spastic paraplegia.

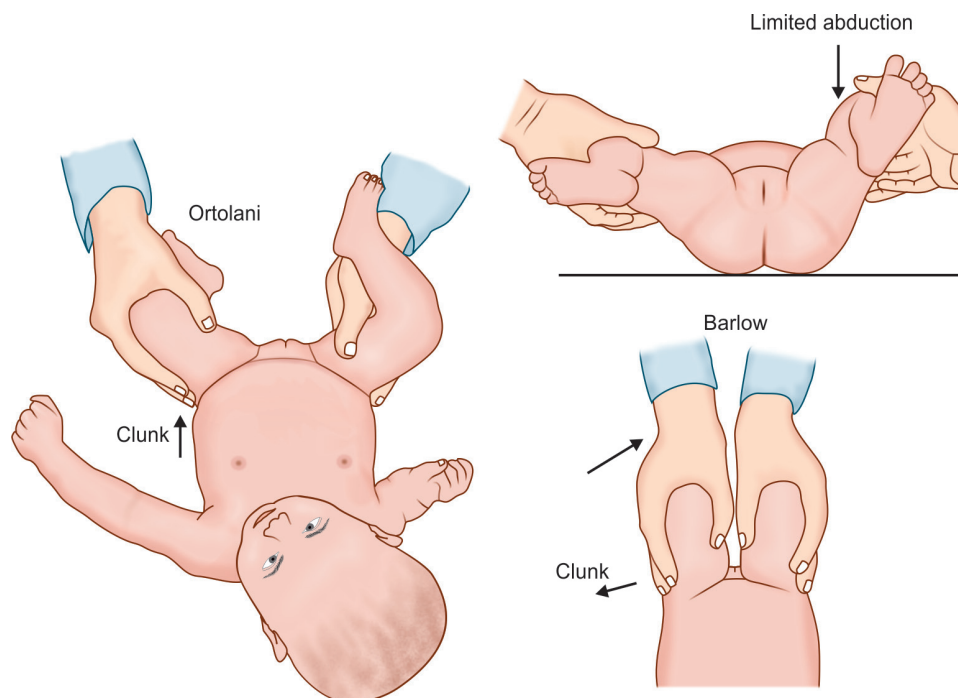


Fig. 47.2: Developmental dysplasia of the hip. Note asymmetrical abduction due to limited abduction of the infant's left hip (top), demonstration of the Ortolani maneuver (left) and Barlow maneuver (right).

Treatment

Treatment is close reduction and maintenance of the correction in position of abduction and flexion. Open reduction may become necessary if diagnosis is made late or if closed reduction has yielded unsatisfactory result.

Prognosis

Without treatment, delay in learning to walk may occur. If dislocation is bilateral, significant lordosis and waddling gait result. Complications include avascular necrosis, redislocation, acetabular dysplasia or residual subluxation and wound infection and other postoperative complications.

SCOLIOSIS

The term denotes alteration in normal spinal alignment occurring in the anteroposterior or frontal plane. It may be idiopathic (majority), congenital (hemivertebra, wedge vertebra, unsegmented bars, mixed), neuromuscular (cerebral palsy, polio, myopathies), syndromal (neurofibromatosis, Marfan syndrome) and compensatory (leg-length discrepancy). Both clinical and radiologic evaluation both posteroanterior and lateral standing films of whole spine, computed tomography (CT) scan, magnetic resonance imaging (MRI), myelography, tomography is required. Treatment of progressive scoliosis is orthotic or surgical (posterior spinal fusion). Compensatory scoliosis warrants correction of the primary disease such as limb inequality.

KYPHOSIS

The term, **kyphosis**, refers to an enhanced angulation in the thoracic or thoracolumbar spine in the sagittal plane or a

roundback deformity. It may be postural (roundback), congenital or idiopathic (Scheuermann's disease). Clinical and radiologic evaluation is necessary. Treatment is orthotic and/or operative.

GENETIC SKELETAL DYSPLASIAS

Osteogenesis Imperfecta

This is the most common hereditary osteoporotic syndromes and is characterized by fractures and skeletal deformities. At least four types are recognized.

1. **Osteogenesis imperfecta (OI) type I** is an autosomal dominant disorder characterized by osteoporosis and excessive bone fragility with fractures (Fig. 47.3), blue sclerae and conductive deafness (in adolescence/adulthood).
2. **Osteogenesis imperfecta type II**, a lethal syndrome, is characterized by low birth weight and length, hypotelorism with beaking of the nose, extremely short, deformed and bent limbs, broad thighs that are fixed at right angles to the trunk (Fig. 47.4) and crumpled long bones and fractured and beaded ribs in X-ray studies. Whereas 50% are born dead (stillbirths), the remaining 50% die soon after birth due to respiratory insufficiency as a result of defective thoracic cage. Though a small proportion has autosomal recessive inheritance, most cases represent new autosomal dominant mutations. Prenatal diagnosis is through a combination of ultrasonography, X-rays and biochemical studies.
3. **Osteogenesis imperfecta type III**, an autosomal recessive disorder, is characterized by multiple fractures and blue sclerae which tend to become less blue with age (Fig. 47.5).



Fig. 47.3: Osteogenesis imperfecta tarda. Note the deformities secondary to multiple fractures. Blue sclera and deafness develop later.

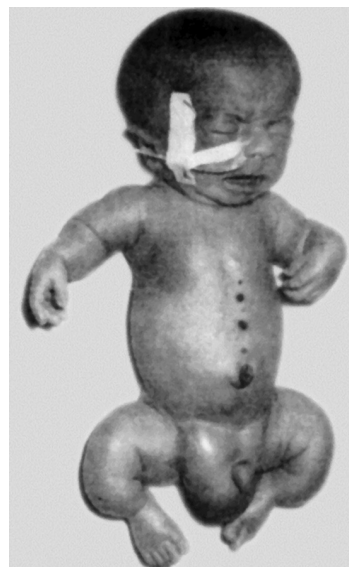


Fig. 47.4: Osteogenesis imperfecta type II.



Fig. 47.5: Osteogenesis imperfecta type III.

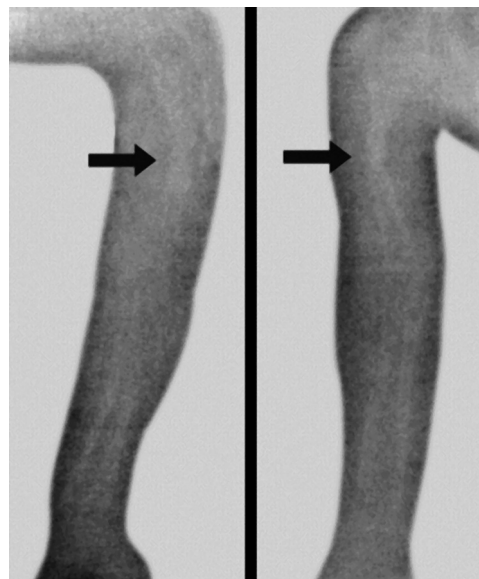


Fig. 47.6: Osteogenesis imperfecta. Radiologic picture depicting fractures.

5. **Osteogenesis imperfecta type IV**, an autosomal dominant disorder, manifests any time from birth to adult life with fractures and deformities. The sclerae show a tendency to become less blue with age. Deafness is less frequent. In some cases, opalescent dentin may be observed.

Radiologic skeletal survey is mandatory for delineation of fractures and deformities (Fig. 47.6). Management of OI types I, III and IV consists of careful nursing on a firm mattress or pillows (for neonates) and prompt splinting of fractures and correction of deformities.

Marfan Syndrome

It is characterized by arachnodactyly (abnormally long limbs, fingers and toes) as seen in (Figs 47.7 and 47.8), subluxation of the lens, hypotonia and hyperextensible

joints, cardiovascular disease such as aortic aneurysm, mitral valve prolapse and other anomalies. Intelligence remains normal.

Upper/lower segment ratio after maturity is remarkably low. Length of middle finger is more than 1.5 times of its metacarpal. Fifth finger may show clinodactyly. Great toe is typically long. Ask the patient to close his fist and try to enclose the thumb within it. You would find that it protrudes beyond the medial edge of the hand. This is called **Steinberg sign**. In the so-called wrist sign, thumb and the little finger clearly overlap when encircling the wrist.

Homocystinuria is an important differential diagnosis and must be ruled out by demonstrating a negative urinary cyanide-nitroprusside test or specific amino acid studies. It is a generalized mesodermal dystrophy and may be inherited as a dominant trait. Around 15–30% cases are sporadic with



Fig. 47.7: Marfan syndrome.



Fig. 47.8: Note the arachnodactyly in Marfan syndrome.

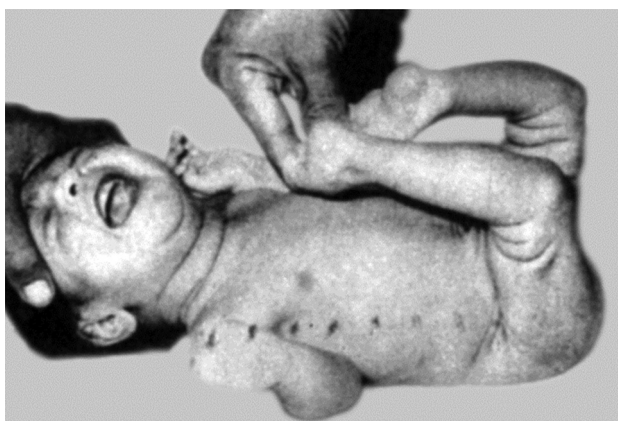


Fig. 47.9: Arthrogryposis multiplex congenita.

new mutation. Each child of an affected individual runs 50% risk of inheriting the number 15 chromosome with the Marfan mutation and thus being affected. Marfan syndrome has an adverse effect on the sufferer's longevity.

Arthrogryposis Multiplex Congenita

It refers to the congenital contractures of multiple joints (Fig. 47.9). Fibrous tissue replaces the affected muscles,



Fig. 47.10: Achondroplasia.

partially or completely. Skin is usually thickened and other deformities like clubfoot may be there.

Besides the major form, **amyoplasia**, which is considered the classical syndrome, there are several other mild or incomplete forms of the disease. Familial occurrence is reported. Etiologic hypothesis include a neuropathic origin supported by reduced number of anterior horn cells and a myopathic origin supported by diminution of movements *in utero*. Treatment is correction of orthopedic deformities followed by rehabilitation.

Achondroplasia

Achondroplasia, an autosomal dominant disorder, is characterized by severe short stature, short trunk and extremities with dominant shortening of the proximal segment (rhizomelia) (Fig. 47.10). Intelligence is normal. Bowed legs, waddling gait, short and stubby fingers of nearly same size, large head with prominent forehead, and depressed bridge of nose, hypoplasia of the maxilla with relative mandibular prognathism, dental malocclusion with anterior open bite and lumbar gibbus which is replaced in the second year by a lumbar lordosis, recurrent otitis media, conductive hearing loss, sleep apnea and sudden infant death syndrome are other common associations.

The thickness of the bones and presence of irregular epiphyseal ends in X-ray is a characteristic feature of achondroplasia. Complications include hydrocephalus, advanced bowing of legs, severe lumbar kyphosis or lordosis cervical or lumbar spinal cord compression. Physiotherapy and bracing in early childhood may ameliorate severe deformities of spine. Severe progressive leg bowing may be corrected by osteotomies in preadolescence or adolescence.

PSEUDOACHONDROPLASIA

This condition is a spondylometaphyseal dysplasia and has four types. It has a striking peripheral similarity to achondroplasia, a spondylometaphyseal dysplasia.



Fig. 47.11: Osteopetrosis. Note the characteristic marble-like appearance of the dense bones.

Osteopetrosis (Marble Bone Disease)

Definition

This extremely rare familial disease is characterized by excessive deposition of calcium in the medullary cavity of the bones which are dense (Fig. 47.11), brittle and vulnerable to fractures.

Etiopathology

The cause is malfunctioning osteoclasts, leading to excessive calcium deposition in medullary cavity.

Types

At least, nine forms are recognized, the most prominent being:

- Osteopetrosis with precocious manifestations
- Osteopetrosis with renal tubular acidosis
- Osteopetrosis tarda (Albers-Schönberg disease)
- Pyknodysostosis
- Dysosteosclerosis.

Clinical Features

Mild disease may remain asymptomatic. Children with severe disease have growth retardation, anemia, hepatosplenomegaly, fractures and deformities. Compression by extra bone may cause blindness, deafness and facial paralysis.

Differential Diagnosis

It includes hypervitaminosis D, Caffey disease, hypoparathyroidism, fluoride intoxication, myelofibrosis, leukemia and sickle cell anemia.

Treatment

Therapeutics include vitamin D, gamma interferon, erythropoietin and steroids. Specific treatment of fractures and deformities is also needed. Only dependable cure lies in bone marrow transplantation.



Fig. 47.12: Caffey disease. Note the enormous periosteal reaction with thickening of the long bone.

Infantile Cortical Hyperostosis

(Caffey Disease)

Definition

An autosomal dominant disease, infantile cortical hyperostosis is characterized by nonsuppurative, tender swellings of flat and tubular bones with tendency for fractures and deformities.

Clinical features

Manifestations, usually appearing about 5–6 months of age, include irritability, fever, myelopathic anemia, hepatosplenomegaly, lymphadenopathy, dwarfism, impaired vision and hearing, painful and tender swellings of bones and occasionally deformities.

Diagnosis

X-ray of affected bones show lamellated periosteal reactions along with soft tissue swelling (Fig. 47.12). Classic picture involves the ulna, clavicle, scapula or mandible. Over a period of time, the bone remodels itself and normal picture returns.

Treatment

Usually, no specific treatment is indicated.

Prognosis

Usually, a self-limited benign disease.

Osteochondritis

The term refers to a group of noninfective and noninflammatory bony lesions in which a vascular disturbance in epiphyses or ossifying centers appears to be the likely cause (Table 47.1).

Perthes' disease is an osteochondritis secondary to a self-limiting avascular necrosis of the head of the femur and causing painful limp in children aged 5–10 years. Major dif-

Table 47.1: Important osteochondritis

Osteochondritis	Bone involved
Perthes' disease	Upper femoral epiphysis
Sinding-Larsen and Johansson disease	Patella
Osgood-Schlatter disease	Tibial tubercle
Scheuermann's disease	Vertebral bodies
Kienbock disease	Lunate
Sever disease	Calcaneum
Köhler disease	Tarsal navicular

Box 47.1**Leading causes of limb (usually leg) length discrepancy**

- **Congenital:** Developmental dysplasia of the hip, hemiatrophy/hemihypertrophy, congenital skeletal limb deficiency (phocomelia), coxa vara.
- **Developmental:** Perthes' disease
- **Neuromuscular:** Poliomyelitis, hemiplegic cerebral palsy.
- **Infections:** Acute pyogenic osteomyelitis.
- **Trauma:** Premature epiphyseal closure following physical injury, malunion of fracture with gross overlapping, angulation and shortening, overgrowth.

ferential diagnosis is tuberculosis of the hip joint though bilateral disease needs to be differentiated from congenital hypothyroidism, sickle cell anemia, mucopolysaccharidosis and multiple epiphyseal dysplasia. Orthopedic treatment is osteotomy (femoral or innominate) for improvement of containment of head in acetabulum.

Limb Length Discrepancy

Etiology

Box 47.1 lists the important causes of limb (usually leg) length discrepancy.

Evaluation

Determination of bone age is important for a relatively accurate assessment of remaining growth of the affected limb. The ultimate discrepancy at maturity can be determined from scanographic and bone age data employing one of the growth remaining tables, the most widely used being Moseley straight line graph. In addition, radiographic evaluation using orthoroentgenogram, scanogram and CT scan can be done.

Treatment

A shortening between 1 cm and 2.5 cm needs compensatory shoes with raised heel and sole. For a shortening exceeding 15 cm, an extension prosthesis is the choice. In cases with a shortening varying between 3 cm and 15 cm, surgical equalization by osteotomy and distraction is today preferred over periosteal stripping which has much less predictability.

CHILD ABUSE AND NEGLECT

For details, See Chapter 6 (Developmental, Behavioral and Psychiatric Disorders).

INFECTIONS/INFLAMMATIONS OF BONES AND JOINTS

Acute Septic (Pyogenic) Arthritis

Etiopathogenesis

It may result from a host of pathogens. *Staphylococcus aureus* (the most predominant), *Streptococcus pneumoniae*, *Gonococcus*, *Meningococcus*, *Escherichia coli* and *Hemophilus influenzae* or as a part of acute infectious disease such as septicemia, enteric fever, pneumonia or influenza.

Route of entry of pathogens may be hematogenous from a primary focus, an infection in the joint *per se* (especially in case of intra-articular metaphysis as in hip and shoulder joints) or a puncture wound.

Clinical Features

Joints involved in order of frequency are knee, hip, elbow and shoulder. Usual presenting features are painful swollen joint with marked restriction of movements of the limb, which is held in a position of flexion.

Diagnosis

In the early stage, X-ray of the affected joint may be normal or show a soft tissue swelling and increase in the joint space compared to the corresponding other joint. In later stage, there is definite diminution in joint space, destruction of cartilage, new bone formation and, finally, full bony ankylosis.

Aspirated fluid from the affected joint is consistent with features of pyogenic arthritis. Differential diagnosis is mainly from acute osteomyelitis, acute rheumatic fever, acute rheumatoid arthritis and tuberculous arthritis.

Treatment

It consists of promptly administering appropriate broad-spectrum antibiotics, including penicillinase-resistant, parenterally, joint aspiration, open drainage of the joint (arthrotomy) and immobilization of the limb by plaster of Paris (POP) or traction. As soon as pain and fever subside and the joint appears quiescent, mobilization of the joint should be initiated.

Osteomyelitis

Etiopathogenesis

The most common etiologic agent is *Staphylococcus aureus*. Additional organisms are group B streptococci and coliforms in neonates, *Hemophilus influenzae* type B in infants and children under 5 years (more so under 3 years), *Pseudomonas aeruginosa* in osteomyelitis following puncture wound of the foot, *Salmonella* species in osteomyelitis associated with sickle cell disease, *Serratia species* and *Aspergillus* species in chronic osteomyelitis, anaerobes in osteomyelitis complicating infections following injury, human bite and decubitus ulcers and fungal infections in osteomyelitis in penetrating wounds, in immunosuppression and in neonates.

838 Acute osteomyelitis occurs as a result of hematogenous spread from a distant focus such as umbilicus, skin or throat, or direct spread from a nearby septic focus. Metaphysis is the most susceptible site on account of sluggish circulation and lack of phagocytic cells. Following bacterial infection, an inflammatory exudate collects under pressure in bone marrow and cortex. What ensues is ischemic infarction of the bone because of septic thrombosis and compromised vascular supply. Formation of periosteal pus elevates the intact periosteum. Serious depletion of blood supply leads to infarction and necrosis of cortical bone, the so-called **sequestrum**. The subperiosteal abscess may even burst through the periosteum into the soft tissues and skin *via* sinus tracts. Simultaneously, inflammatory reaction in the overlying soft tissues leads to signs of inflammation near the location of osteomyelitis. In infants, inflammatory process has a tendency to extend to epiphysis as well, causing septic arthritis.

Chronic osteomyelitis follows inadequately treated acute osteomyelitis. It has ischemia and poor host defenses as compared to the high virulence of the pathogens, more so in the presence of a foreign body or necrotic tissue, as predisposing factors.

Clinical Features

Acute osteomyelitis manifests with fever, toxemia, pain, local signs of inflammation (warmth, tenderness and swelling), and pseudoparalysis. In neonates, there is a greater tendency to have multifocal disease with involvement of the adjacent joints. Often, signs are nonspecific or few. Vertebral osteomyelitis is characterized by referred pain to abdomen, thigh or hip.

Chronic osteomyelitis is characterized by local manifestations including sinus tract. The discharging sinus is fixed to the underlying bone. Adjacent joints may be stiff because of secondary arthritis.

Diagnosis

Isolation of the etiologic agent by blood culture, or culture of material obtained by bone aspiration or biopsy is the most important diagnostic tool. Culture must include anaerobes.

Plain X-ray shows characteristic changes in the form of periosteal elevation, subperiosteal new bone formation, rarefaction of bone in second week only (usually 10–14 days). In the first week, a deep soft tissue swelling with obscuring of fat lines between muscles do suggest osteomyelitis. A three-phase bone scan, radionuclide scan, CT scan or MRI may be reserved for difficult case.

Other investigations include acute phase reactions like total leukocyte count/differential leukocyte count, erythrocyte sedimentation rate and C-reactive protein, and tests for tuberculosis in case tuberculous etiology is on the card.

Differential Diagnosis

Osteomyelitis needs to be differentiated from a multitude of conditions, say cellulitis, abscess, bursitis, pyomyositis, septic arthritis, hemophilia, acute rheumatism, trauma, diskitis and malignancy, etc.

Treatment

As soon as a clinical diagnosis of acute osteomyelitis is made, intravenous antibiotic therapy must be started. A strong anti-staphylococcal antibiotic (cloxacillin, nafcillin, oxacillin, vancomycin in case of organisms resistant to former agents) should be administered. In neonates, it should be supplemented with an aminoglycoside (gentamicin) to cover Gram-negative organisms. Alternatively, cefotaxime may be given.

In children under 5 years, especially when osteomyelitis is accompanied by septic arthritis suggesting *Hemophilus influenzae* type B infection, anti-staphylococcal antibiotic should be given in combination with an anti-*Hemophilus influenzae* type B antibiotic (chloramphenicol). Alternatively, cephalosporins, such as cefuroxime or ceftriaxone, which cover both these organisms may be employed.

In osteomyelitis following puncture wound of foot, antistaphylococcal penicillin should be supplemented with antipseudomonal penicillin (ceftazidime) and an aminoglycoside. Osteomyelitis with sickle cell disease should be treated with anti-staphylococcal antibiotic with a cephalosporins (cefotaxime) or an aminoglycoside.

For anaerobic organisms, the recommended drug is clindamycin. In uncomplicated cases showing encouraging response, IV antibiotic should be given for 6 weeks followed by oral antibiotics in high doses for 12 weeks. Adjuvant therapy includes analgesic/anti-inflammatory agents, nutrition, hydration and immobilization.

TUBERCULOSIS OF BONES AND JOINTS

Tuberculous involvement of bones and joints usually occurs following hematogenous spread from the primary focus, which is generally in the lungs.

- In tuberculous osteomyelitis, the bones frequently involved are short long bones (metacarpals, metatarsals, phalanges) and short bones (calcaneum, carpals). Involvement of long bones is very infrequent.
- In tuberculous arthritis, commonly affected joints are hip, knee and elbow, the infection being either synovial or osseous. Tuberculosis of spine (Pott's spine) usually involves thoracolumbar spine because of excessive mobility of the region and proximity of cisterna chyli, which may bring tuberculous foci from the mesenteric lymph nodes. Site of vertebral involvement in order of frequency is metaphyseal, central, appendiceal and anterior. Most common deformity is kyphosis (knuckle, angular or rounded). Locally a prevertebral or paravertebral abscess may be present or, else, it may present elsewhere (psoas abscess, lumbar abscess, chest wall abscess, gluteal abscess). For paraplegia secondary to Pott's spine, See Chapter 28 (Pediatric Neurology).

Besides ATT See Chapter 21 (Protozoal Infections and Infestations) Orthopedic treatment consists in immobilization, drainage of the abscess (preferably by surgical procedures like costotransversectomy, anterolateral decompression, radical operation or laminectomy) and arthrodesis (fusion) of the joint.

TRANSIENT SYNOVITIS OF THE HIP (Observation Hip)

It is sterile inflammation and effusion of the hip joint, often preceding septic arthritis or Perthes' disease, characterized by painful hip with restriction of movements (especially internal rotation). Unlike septic arthritis, it does not cause toxemia. Diagnosis is from ultrasonography and, at times, aspiration of the hip joint. Treatment is immobilization of the joint. Within a week, it resolves.

RHEUMATOID ARTHRITIS

For details, See Chapter 35 (Pediatric Rheumatology).

BONE TUMORS

Box 47.2 presents classification of benign growths and true tumors in relation to bones.

PEDIATRIC SPORTS MEDICINE

Participation in games and sports is vital for physical fitness, psychosocial development, decision-making, self-confidence and overall health and personality of the child. At times and in some children, specific advice from the pediatrician becomes mandatory regarding the magnitude of restriction, type of recommended sport activity, and fitness for return to normal activity and participation in sports.

Indications for Restriction

The pediatrician must use a balanced restraint in advancing advice for restriction of sports activity. The major indications for such a restriction are:

- A **definite need**, e.g. fracture, major illness in which physical exercise may worsen the patient's condition.
- A **relative need**, e.g. atlantoaxial instability in which contact (collision) sports are not permitted but noncontact sports are allowed.

Categorization of Sports

- **Contact/collision:** Hockey (both field and ice), football, wrestling, boxing, judo, karate.
- **Limited contact/collision:** Basketball, baseball, gymnastic, skating (both roller and ice), squash, handball,

volleyball, skiing, horseback riding, bicycling, driving, 839 high jump.

- **Noncontact/strenuous:** Swimming, running, lawn tennis, weight lifting, aerobic dancing, javelin, shot put.
- **Noncontact/moderately strenuous:** Badminton, table tennis.
- **Noncontact/nonstrenuous:** Archery, golf, riflery.

Areas of Concern

These are categorized as under:

- **Orthopedic:** Knee or ankle injury, subluxing patella, scoliosis, cervical spine abnormality, chondromalacia patella.
- **Cardiovascular system:** Murmur, hypertension, rheumatic heart disease, congenital heart disease, arrhythmias.
- **Pulmonary:** Exercise-induced asthma, obstructive lung disease.
- **Anatomic:** Absence of eye, kidney, testis, organomegaly.
- **Hematologic:** Anemias (including thalassemia major and sickle cell disease, bleeding disorder).
- **Dermatologic:** Contagious diseases like herpes simplex, chickenpox, etc.
- **Neurologic:** Mental retardation, seizures, syncope, repeated head injury.

Disqualifications and Limitations

Every child has a right to participate in sports. The parents need to be advised by the attending doctor with this fundamental principle in mind. Too stringent and confining restrictions often do harm to the child, especially to his psyche. Attempts must always be made to find out appropriate alternatives for an unavoidable restriction. For instance, a child may have to be off from strenuous and contact sport such as boxing for an unavoidable reason. But, then, he can be shifted to noncontact but moderately strenuous badminton.

Pediatric Evaluation

Every child ought to have a good pediatric checkup before he takes up a regular sport. The objective of such a pre-participation health examination is to identify specific conditions which are likely to place the child at risk for injury, exacerbation of his condition, or even death. Such an examination needs to be conducted periodically or when there is a change in the level of competition, e.g. change from a junior group to a senior group.

Pediatric examination should also include psychologic assessment with a spotlight on determining attitudes and behaviors pointing to risks of burnout or overuse injuries. Pediatrician's advice for rest, rehabilitation, and returning to the field after a reasonable gap of time must be sought.

The Pediatric Sports Medicine Program and the Pediatrician's Responsibilities

- To assess the frequency, type and duration of physical activities during health supervision visit.

Box 47.2 Classification of bone growths/tumors

Benign tumor-like lesions

- **Reactive:** Benign osteoblastoma, osteoid osteoma, non-osteogenic fibroma
- **Cystic:** Solitary cyst, aneurysmal cyst
- **Hamartoma:** Osteoma, osteochondroma (solitary exostosis), enchondroma.

True tumors

- **Primary:** Osteosarcoma, chondroblastoma, chondrosarcoma, chondromyxoid fibroma, fibrosarcoma, malignant fibrous histiocytoma, plasma cell myeloma, Ewing tumor, lymphomas, osteoclastoma
- **Secondary:** From primary malignancy of other sites.

- 840** ■ To develop the capacity to perform body composition analysis by skinfold testing. Obese children who require to lose weight should be monitored.
- To teach the importance of regular physical activity (moderate to vigorous) as a means of safeguarding against illness during adulthood.
 - To encourage parents to serve as role models by participating in regular physical activity along with the child.
 - To work with community schools, to support daily physical education in these schools and to promote moderate to vigorous activity tasks in physical education classes.

PEDIATRIC FRACTURES

Fractures account for one-sixth of pediatric injuries; the common ones being clavicular, distal radius and ulna, humerus, phalangeal, lateral malleolar, metatarsal, toe phalanges and toddler fractures.

Special Features

Their distinct peculiarities compared to adult fractures on account of major anatomic, physiologic and biochemical differences. Fracture remodeling occurs by a combined

action of periosteal reabsorption and new bone formation. Overgrowth by 1–3 cm, especially in femur, in children under 10 years warrants bayonet apposition. Angular deformities, shortening or both occur because of closure of physes. Fracture healing is more rapid owing to high growth potential and thicker and more active periosteum.

Patterns

These may be complete (most common), greenstick, buckle (torus), plastic deformation (bend), and epiphyseal which are further subdivided into five groups for prognostic predictions.

Management Highlights

Immobilization (simple, splint, POP cast, figure-of-eight strap in clavicular fractures) is central to treatment of pediatric fractures. A close reduction may be warranted in some cases. Indications for operative stabilization include:

- Displaced epiphyseal fractures
- Displaced intra-articular fractures
- Unstable fractures
- Fractures in the multiply injured child
- Open fractures.

Multiple Choice Questions

1. Syndactyly is a feature of each of the following, except:
 - A. Laurence-Moon-Biedl syndrome
 - B. Trisomy 21, 13, 18
 - C. Carpenter syndrome
 - D. Apert syndrome
 - E. Refsum syndrome
2. Positive Barlow test is a feature of:
 - A. Congenital pseudarthrosis of the tibia
 - B. Developmental dysplasia of the hip
 - C. Marfan syndrome
 - D. Arthrogryposis multiplex congenita
3. Spot the wrong entry:
 - A. Blue sclera and deafness are early features of osteogenesis imperfect
 - B. No treatment is needed for cleidocranial dysostosis
 - C. A persistent bow leg deformity needs orthopedic intervention
 - D. Scoliosis may occur in cerebral palsy from neuromuscular involvement
 - E. Even without treatment prognosis in osteopetrosis is good in most cases
4. True observations about sports medicine include each of the following, except:
 - A. Contact/collision sports include hockey, football, wrestling, boxing, judo, karate, etc
 - B. Noncontact/strenuous sports include archery, golf and riflery
 - C. Restriction for contact sports is not needed even in atlantoaxial instability
 - D. Contagious diseases like herpes simplex, and chickenpox are areas of concern
 - E. Every child needs to have a good pediatric checkup before takes up a regular sport
5. Each of the following is a feature of transient synovitis of the hip, except:
 - A. A sterile inflammation
 - B. Often follows Perthes' disease
 - C. No toxemia
 - D. Treatment is immobilization
 - E. Resolution within a week

Answers

1. E 2. B 3. A 4. C 5. B

Clinical Problem-solving

Review 1

A 12-year-old girl, an average student of class 7, presents with excessive tallness (height 162 cm), abnormally long fingers and toes, hyperextensible joints and deteriorating vision.

1. What is the most likely diagnosis?
2. What is the closest differential diagnosis? How will you exclude it?
3. What is the risk of this illness in the offsprings?

Review 2

A 2-month-old infant being treated for staphylococcal lobar pneumonia with ampicillin plus cloxacillin develops high fever with inflammatory swelling of the metaphysis of the right femur.

1. What according to you should be the diagnosis?
2. Why did this child develop this complication in spite of being treated with ampicillin and cloxacillin which are known to be effective in staphylococcal pneumonia?
3. Why is metaphysis more vulnerable to such a complication?

Answers

Review 1

1. Marfan syndrome, a generalized mesodermal dystrophy.
2. Homocystinuria which is excluded by demonstrating a negative sodium pruside specific amino acid studies.
3. The offspring of an affected individual run 50% risk of inheriting the number 15 chromosome with Marfan mutation and thus getting affected.

Review 2

1. Acute osteomyelitis as a complication of Staphylococcal pneumonia.
2. The problem of multidrug resistant strains of Staphylococcal aureus seems to be responsible for poor response to ampicillin and cloxacillin.
3. Metaphysis is the most vulnerable site for acute osteomyelitis as a result of hematogenous spread from a distant focus on account of a sluggish circulation and lack of phagocytic cells.

FURTHER READING

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SECTION 7

Miscellaneous and Unclassified Issues

Section Outline

- 48. Miscellaneous and Unclassified Issues

CHILD ADOPTION

The term, **adoption**, is employed to an act of affiliation by virtue of which a child is removed from the biological parents and is placed in the adoptive family. The adoptive parents become responsible for his care and welfare.

Why Adoption?

The most common reason for adoption is a viable alternative means for attaining parenthood by a childless couple. Other reasons could be eagerness of a couple to provide home to a homeless child, an incurable genetic disorder in couple's biologic child, a desire for a child of the other sex, advanced age of the mother/parents. The parents are expected to adopt a child because they love to take his care and not because they see a support in him for their old age.

Most children that are available for adoption come from young unwed mothers who fail to keep such children with them because of the stigma attached to out-of-wedlock issues. Remaining reasons for giving the child away for adoption include desertion by one parent, death of a parent, birth of an unwanted child (usually a girl or a handicapped child).

Source of Adoption: A Relative or an Agency?

Though most often adoption is restricted to the couple's relatives, this is, by no means the recommended means of adoption. Neither taking resort to private adoptions through hospitals and medical practitioners without completing the legal formalities is in order. Such an adoption can never guarantee confidentiality. Today, moreover, biologic parents can anytime contest the adoptive parents' right to continue with the custody of the child.

The best way to adopt a child is through the reputed adoption agencies, children's homes and other institutions that have children for adoption. These agencies make available to the adopting couple the requisite details about the exact procedure for adoption. The agencies make sure that the adopted child is smoothly placed with the adopting parents.

Adoption Laws

The well-known Hindu Adoptions and Maintenance Act 1956 governs adoption among the majority community in India. In case of minority communities whose personal laws fail to permit adoption, the parents can only be guardians to the adopted children. Here, the adopted

Box 48.1 Highlights of the adoption law***In respect of the child***

- A prospective child for adoption must not have completed 15 years.
- An adopted child cannot be readopted by another person even though the latter is the child's natural (biological) parent.
- A married child cannot be adopted.

In respect of the adopting parent

- A Hindu cannot adopt more than one male or a female child.
- The adopting parent must be a "major" (has completed age of 18 years) and of sound mind.
- It is obligatory for a married Hindu male to obtain consent of his wife for adopting a child.
- A married Hindu woman cannot adopt even with the consent of her husband.

In respect of parent who give in adoption

- The father cannot give his child in adoption without the consent of the mother.
- The mother of an illegitimate child is entitled to give the child for adoption.

In respect of the guardian

The guardian is entitled to give the child in adoption under special circumstances such as when the parentage is not known, e.g. abandoned children in hospital, nursing home or refugee camp.

child does not automatically get the status of a biologic child. Some other notable features of the adoption law are summarized in Box 48.1.

The adoption laws have been criticized for some glaring deficiencies which leave a room for violation of the laws by various quarters including the Apex Court. For instance, a married Hindu woman is not entitled to adopt a child notwithstanding consent from her husband. Secondly, an adult orphan cannot be adopted because he has no guardian. Thirdly, an adopted child has got to break all relations with biologic parents and can never return to them even when he opts for this course as he grows up.

Adoption and the Pediatrician

The role of the pediatrician both before and after adoption remains important. He must encourage adoption from an approved agency only. He should appropriately assess the psychosocial settings of the adopting couple. Secondly, he should provide adequate safeguard to the adopting couple by providing correct information about the health status of the child to be adopted. Thirdly, he should make available to the family benefit of his advice for the emotional problems of the adopted child as a consequence of overindulgence of the parents.

846 INFANTILE TREMOR SYNDROME

An obscure entity, characterized by tremors, anemia and regression of milestones in Indian infants and young children, is termed **infantile tremor syndrome (ITS)**. It was first described in 1957 by Dikshit who called it **nutritional dystrophy and anemia**. In the subsequent years, it has been reported from various parts of the country, more so from south India, Jabalpur, Lucknow, Punjab, Chandigarh, Simla and Jammu. A few cases were seen among Bangladesh refugees during 1971–72.

“Infantile meningoencephalitis”, “tremor syndrome”, “nutritional tremor syndrome”, “syndrome of tremors, mental regression and anemia in infants” and “syndrome of tremors in infants” rank among the other nomenclatures employed for this disease in the literature.

Epidemiologic Considerations

- **Incidence:** It accounts for 1–2% of pediatric admissions in the hospitals that have started recognizing this condition. In our experience, it formed 1.9% of the admissions to the pediatric inpatient department of the Snowdon Hospital, Shimla, during 1971–74. At Jammu, recently, at one time, 6 of our 200 hospitalized children happened to suffer from ITS. This may be little exceptional. But, then, nearly always we have at least one or two such patient around.
- **Age:** The vast majority of the cases fall in 6 months to 1½ years age group. A few children may be up to 2 years of age. It is unusual to see cases outside this age range. This author has seen a 3-year-old and another aged 5 years with characteristic features of this syndrome.
- **Sex:** Males suffer more frequently than females.
- **Nutritional background:** These infants come from poor families. Most of them are breastfed and have concomitant malnutrition, especially anemia, though they look plump.
- **Seasonal variation:** The peak incidence is noticed during summer.

Etiology

Three hypotheses have been put forward:

1. **Nutritional:** Earlier reports suggested that ITS appeared to result from megaloblastic anemia which responded well to vitamin B₁₂. This hypothesis received support from the following:
 - Megaloblastic anemia was always associated with ITS.
 - These infants had low levels of vitamin B₁₂
 - The administration of vitamin B₁₂ to these patients led to regression of the major manifestations of ITS
 - The syndrome resembled cases of megaloblastic anemia with neurologic manifestations seen in Italy and America.

During recent past, it has been observed that not all infants with ITS suffer from megaloblastic anemia. In fact, some do not have it at all while others show dimorphic anemia. There are cases seen by us as well as others who have purely iron-deficiency anemia.

Moreover, even those suffering from megaloblastic anemia may need folic acid alone or in combination with vitamin B₁₂ for adequate response. At the same time, infants without megaloblastic anemia, may not need vitamin B₁₂ and folic acid and yet evince cure with correction of iron deficiency anemia and improvement in the overall nutritional status.

Even magnesium deficiency has been blamed as another possible etiologic factor. In fact, some workers have found reduced magnesium in chronic fatigue syndrome (CFS) of infants suffering from ITS. Tremors and rigidity, among other neurologic manifestations, are known to result from such deficiency. How far magnesium lack contributes to the development of ITS is difficult to say. Zinc reduction in body tissues and fluids is documented by us and others. In view of presence of anemia, pigmentation, hair changes, tremors and mental lethargy, role of zinc deficiency in its etiology appears quite probable.

2. **Viral encephalitic:** It has been suggested that ITS may well be a sort of viral encephalitis. Acute onset of tremors and their occurrence following intravenous drip or blood transfusion in certain instances are often cited in support of this hypothesis. However, no virus has so far been isolated. Also, absence of any consistent CSF change and course of illness do not lend support to this speculation.
3. **Degenerative:** Recently, brain biopsies and pneumo-encephalographic studies have revealed cortical atrophy in majority of the cases investigated in Lucknow and Patiala. The Patiala workers have found patchy fibrosis of muscle tissue and demyelination and swelling of the myelin sheath of nerves. Similar brain, muscle and nerve alterations have been seen by us on autopsy material.

Clinical Features

A typical infant with ITS is plump (though underweight for his chronologic age), apathetic and anemic with hair and skin changes (Fig. 48.1).



Fig. 48.1: Infantile tremor syndrome. Note the hair changes, vacant look, chubby appearance despite malnutrition and tremors.

Hair is light-colored (*hypochromotrichia*) and sparse as in kwashiorkor. There is a brownish reticular **pigmentation of skin**. This is more remarkable over dorsal aspect of hands (especially over terminal phalanges), feet, knees, ankles, axillae, buttocks, lower abdomen and medial aspect of thighs. There is history of regression of motor and mental milestones in the recent past. The onset of tremors is preceded or accompanied by some stress in the form of acute lower respiratory infection (ALRI) or gastroenteritis. These tremors usually disappear during sleep in most cases; in others their intensity remarkably diminishes.

Tremors resemble those seen in Parkinsonism and appear to originate from cortical neurons. These may be generalized but are more prominent in distal parts of the limbs (especially upper limbs), head, face and tongue. Even trunk may be involved. Some infants produce tremulous cry like that of a lamb. They keep tossing their head from side to side with the saliva drooling from mouth and have dull, expressionless look. Mental and motor development is impaired in all.

Hypotonia, particularly of thigh muscles, is common though hypertonia may be found in an occasional patient. **Anemia** is generally moderate and may be macrocytic/megaloblastic, normocytic-normochromic, iron-deficiency or dimorphic type. Incidence of variable **nutritional deficiencies** and superadded infestations/infections, including tuberculosis, is high. **Incomplete forms**, say the so-called **pretremor state**, with all the features of the syndrome minus tremors are also known. We have observed development of tremors in such untreated infants in due course.

Course

Three phases are recognized:

1. **Pretremor (prodromal) phase** is characterized by regression of attained milestones, motor and/or mental slowness with vacant expressionless facies, anemia, pigmentation, hair changes, plumpy look despite malnutrition and drooling. Tremors are absent.
2. **Tremor or classical phase** is characterized by appearance of tremors on top of clinical features of pretremor state. Initially, the tremors are seen only on crying or feeding and involve fingers, face and tongue. Subsequently, these become generalized.
3. **Posttremor or recovery phase** is characterized by regression of tremors and other features of the syndrome. The mental dullness continues for several months.

Diagnosis

The familiarity with the clinical picture, described above, together with high index of suspicion should enable a clinician to recognize an infant suffering from this syndrome. Investigations should be aimed at finding the extent and morphologic type of anemia, determining the nutritional status and detecting coexisting infections and infestations.

Electroencephalographic (EEG) in cases with gross tremors shows changes that are no different from those encountered in seizure disorder. The changes are in the

Table 48.1: Drugs employed for controlling tremors

Drugs	Doses
Phenobarbital	3–5 mg/kg/day (O) in one or two doses
Chlorpromazine	2–3 mg/kg/day (O) in three divided doses
Carbamazepine	10–20 mg/kg/day (O) in two divided doses
Sodium Valproate	20 mg/kg/day (O) in two to three divided doses
Propranolol	0.1–1 mg/kg/day (O) in three divided doses

form of high voltage sharp waves and spikes with a slow background activity of delta range which are by and large consistent with those encountered in advanced malnutrition. Interestingly, the EEG changes do not revert to normal after the tremors are fully controlled. We are yet to ascertain if these show disappearance during a longer follow-up.

Treatment

Since anemia and malnutrition are always present (though cause and effect relationship between these and ITS is not as yet definitely established), it is desirable to treat these as discussed elsewhere in this book. We do not favor administration of vitamin B₁₂ to every child with ITS. Zinc in therapeutic doses is strongly recommended.

Administration of phenobarbital orally in the initial stage is advantageous. It reduces the intensity of tremors and may even control these, protects the child from continued exhaustion and provides much needed psychologic relief to the worried parents. Furthermore, it may well help in cutting down the period required for control of tremors. Some workers have reported encouraging response to chlorpromazine, propranolol, carbamazepine, valproate, etc. (Table 48.1) in cases showing poor results with phenobarbital. Along with these measures, the child should receive adequate treatment for his other associated problems like intestinal parasites, respiratory infection or tuberculosis.

Prognosis

With the above measures, response is encouraging. As the nutritional status (including hemoglobin) improves, tremors gradually cease. This generally takes approximately 1–4 weeks. The children continue to be mentally dull and sluggish for quite some months to come.

Electroencephalographic changes seen in advanced cases perhaps take much longer time to regress even though the tremors may be over. ITS per se does not cause death. But fatalities as a result of a coexisting illness are not uncommon.

SUDDEN INFANT DEATH SYNDROME

This term refers to the sudden, unexpected death of an apparently healthy infant, usually 2–3 months of age, who had been put to the bed without any suspicion of such an occurrence. A conventional autopsy fails to reveal the cause of death.

When an apparently healthy infant suffers from an episode in which his breathing ceases, cyanosis or

848 pallor develops, and he becomes unresponsive but is successfully revived (resuscitated), the term, **apparent life-threatening event (ALTE)**, is employed. This state is also called **near-miss** or **aborted sudden infant death syndrome (SIDS)**. In this state, there is a considerable risk of SIDS subsequently. In the event of a SIDS in a family, risk for the next or subsequent infant is 5 times higher than the usual risk.

Etiopathogenesis

Etiology remains obscure. Allergy to cow milk, enlargement of thymus, suffocation, deficiency of parathyroids or adrenals, hyponatremia and fulminant respiratory infection causing laryngeal obstruction and/or spasm figure among the large number of conditions/factors that are incriminated in its etiology. Such states as prolonged sleep, apnea, (associated with central nervous system {CNS} disorders), vascular rings, familial prolongation of QT interval (Romano-Ward and Jervell and Lange-Nielsen syndrome), accidental suffocation and child abuse and neglect (CAN) at times camouflage as SIDS. An abnormality of cardiorespiratory control, in which state of consciousness or CNS activity plays a modulating role, appears to be shared by all cases of true SIDS. Prone sleeping position is an important risk factor for SIDS.

Though the pathologic findings, taken in totality, suggest occurrence of hypoxia preceding the tragic event, autopsy shows no hyperplasia of the carotid bodies.

Diagnosis

In case of infants at risk (low birth weight {LBW}, near-miss, or ALTE, siblings of SIDS cases), history should include information on physiologic handicaps before birth such as low Apgar score, abnormality in control of respiration, heart rate and temperature, and postnatal growth retardation. The parents must be questioned about the infant's feeding, medications, etc.

Physical examination should concentrate on infant's nutritional status, hydration, evidence of infection, CAN and neurologic handicaps. Respiratory system should be particularly evaluated. The infant needs to be observed while he is being fed. Investigations include:

- Blood analysis for glucose, sodium, potassium, calcium, phosphorus, magnesium, blood urea nitrogen (BUN), pH and blood-gas analysis
- Urinalysis
- Microbiologic tests
- ECG monitoring
- Electroencephalogram (EEG)
- Radiology—barium swallow, chest X-ray, skeletal survey
- Esophageal pH studies
- 4–8 hours sleep studies.

Currently, home monitoring technologies utilizing event recordings (respiratory pattern, heart rate, ECG, oxygenation) are being evaluated for prospective identification of risk of SIDS.



Fig. 48.2: Progeria. Note the classical features of premature senility.

Treatment

The parents distressed with guilt feeling need to be assured that they were not the cause of the sudden death of the infant. They also need to be counseled on anticipatory guidance. Use of caffeine and theophylline in apnea of prematurity and infancy may indirectly cut down the incidence of SIDS by improving respiratory pattern in these subjects.

PROGERIA

(Hutchinson-Gilford Syndrome, Plucked Bird Disease, Premature Senility)

First described in 1886 by Hutchinson and Gilford, this is an extremely rare disorder (incidence 1 in 8 million) of unknown etiology though believed to be due to a genetic mutation. The characteristic features include infantilism, remarkable absence or diminution of subcutaneous fat, generalized alopecia (including missing eyebrows) and other manifestations of premature onset of senility (Fig. 48.2). Physical development in infancy is not significantly affected. Mental development is fair enough even when full-blown picture has developed.

Manifestations such as scleroderma, midfacial cyanosis and sculpted nose in early infancy may suggest the existence of the syndrome. Median lifespan is around 13 years, death usually occurring from complications of cardiac or cerebral vascular disease.

Since the patients do not become sexually mature, parent-to-child transmission is not noticed. Prognosis is usually fair. With persistence of lymphedema, subcutaneous tissue undergoes fibrotic changes. Some disfigurement may result.

CHRONIC FATIGUE SYNDROME

(Chronic Mononucleosis, Chronic Epstein-Barr Virus Infection, Immune Dysfunction Syndrome)

The term is applied to a state of easy fatigability accompanied by mild to moderate severe (debilitating) somatic symptoms.

Etiopathogenesis

Most pediatric subjects are adolescents, from both sexes with predominance of girls. The probable cause is an infection with replication of a known or new virus, including Epstein-Barr virus (EBV), influenza virus, varicella, rubella as the inciting factor or nonspecific symptoms of a sore throat, fever, myalgia, diarrhea, etc.

Clinical Features

Chronic fatigue, varying from mild (subtle) to severe (debilitating) is the most predominant manifestation. This is often accompanied by deterioration in work or school performance, activities of daily living, exercise tolerance and interpersonal relationship. There may be a multitude of psychologic or neuropsychiatric complaints. Physical examination hardly shows any abnormal findings.

Diagnosis

It is primarily by exclusion. It is important to have a psychologic evaluation for depression or anxiety. A complete blood count (CBC) with erythrocyte sedimentation rate (ESR), electrolytes, BUN, creatinine, serum alanine transaminase and aspartate transaminase, thyroid function test and urinalysis and stool microscopy are in order to exclude treatable diseases and to reassure the patient.

Treatment

Therapy of CFS is directed toward emotional support for the child and his parents or family and symptomatic measures.

Prognosis

Complete blood count is an illness of a prolonged duration with waxing and waning of symptoms. There is no mortality though significant morbidity is a rule.

GROWING PAINS

This poorly understood entity is characterized by vague, deep aching bodily pains (nonarticular) especially in calves, thighs, behind knees and occasionally in upper limbs. They may be mild or severe. In one-third cases, there may be associated headache and abdominal pain.

The pains are usually complained of toward the late evening and during night. Excessive fatigue and activity precipitate them. The affected subjects usually belong to adolescent or preadolescent age group. In a significant proportion, there is a family history of such pains. It is wrong

to believe that the pains have anything to do with physical growth, epiphyseal closure or hormonal changes. There is good deal of consensus that these may well be “a reaction to emotional disturbances, family pain predisposition or environmental stress”. Excessive fatigue, nutritional deficiency state, and orthopedic defects may also contribute to their development.

The cornerstone of treatment is reassurance to the parents as well as the child that the problem is not organic and will be over in due course. Child's emotional needs must receive adequate attention. His general health may need improvement. Intestinal parasite(s), and anemia, if present, should be treated. Intolerable pains may warrant use of analgesics and local massage.

HISTIOCYTOSIS

The term is applied to a group of rare, but severe disorders having significant proliferation or accumulation of cells of the monocyte-macrophage system of bone marrow origin.

Based on histopathological findings, a diagnostic classification is now available (Table 48.2).

The best known histiocytoses, eosinophilic granuloma, Hand-Schuller-Christian disease and Letterer-Siwe disease, are included in Class I or Langerhans cell histiocytosis (LCH). Single or multiple bone lesions constitute hallmark of this histiocytosis, followed by skin lesions, exophthalmos, pituitary dysfunction and systemic manifestations like fever, weight loss, malaise, failure to thrive (FTT), irritability, anemia and thrombocytopenia secondary to bone marrow infiltration.

In Class II histiocytosis, manifestations include fever, weight loss and irritability, hepatosplenomegaly, aseptic meningitis, CSF invasion with macrophages, hyperlipidemia, hypofibrinogenemias, high hepatic enzymes and very high levels of circulating soluble interleukin-2 receptors.

SARCOIDOSIS

This multisystem chronic granulomatous disorder of adults may infrequently be encountered in childhood.

Etiopathogenesis

The etiology is unknown. The granulomatous lesions may involve any organ or system though lung is the most commonly affected organ with parenchymal infiltrates, miliary nodules and hilar and paratracheal lymphadenopathy. Typically a granuloma contains epithelioid cells, macrophages and giant cells in the center surrounded by a

Table 48.2: Classification with prominent features of pediatric histiocytosis

Classes	Histologic findings	Therapies
Class I (Langerhans cell histiocytosis)	Langerhans cells with Birbeck granules	Local therapy for isolated lesions; chemotherapy
Class II (familial erythrocytic lymphohistiocytosis infection-associated prominent erythrophagocytosis)	Normal reactive macrophages with prominent erythrophagocytosis	Chemotherapy bone marrow transplantation
Class III (malignant histiocytosis, acutemonocytic leukemia)	Neoplastic proliferation of cells with macrophages or their precursors	Antineoplastic chemotherapy characteristics of monocytes (including anthracycline)

850 mixture of monocytes, lymphocytes and fibroblasts. A large proportion of the granulomas heal with complete preservation of the parenchyma. Nevertheless, some 20–25% of the lesions may end up as fibrotic scar tissue.

Clinical Features

These include chronic cough, easy fatigability, weight loss, anemia, lymphadenopathy and liver involvement. In older children, predominant manifestations may be ophthalmic (uveitis, iritis), dermatologic (maculopapular erythematous rash) and arthritic (large, but painless effusions with minimal limitation of movements).

Diagnosis

Screening tests include a high ESR, eosinophilia, hyperproteinemia, hypercalcemia, hypercalciuria, a high Kveim test angiotensin converting enzyme (ACE) level and an intradermal injection of material from a sarcoid lesion (Kveim test). Definitive diagnosis is from a biopsy of the granulomatous lesion.

Differential Diagnosis

It is from tuberculosis, pulmonary fungal infection (mycosis), lymphoma and inflammatory bowel disease and phlyctenular conjunctivitis.

Treatment

It is primarily symptomatic and supportive, at times warranting the use of steroids to suppress acute manifestations.

Prognosis

Those who fail to have spontaneous recovery, after months to years, may develop a progressive pulmonary disease and blindness.

SOME MINOR PROBLEMS OF THE NEWBORN, THE INFANT AND THE YOUNG CHILD

It is not infrequent for the parents to demonstrate undue anxiety over certain minor and basically benign problems. The attending doctor is required to provide proper guidance, reassurance and support to the parents, the mothers in particular, in allaying their concern and running from pillar to post. In this way, many unnecessary investigations and irrational therapies are avoided.

Neonatal Period

The benign problems that cause undue parental anxiety include physiologic jaundice, vomiting, transitional stools, constipation, toxic erythema, milia, Mongolian spots, salmon patches, benign neonatal hemangiomas, harlequin color change, epstein pearls, sucking callosities, subconjunctival hemorrhages, physiologic mastitis, vaginal bleeding, natal teeth, cephalhematoma, caput succedaneum, umbilical hernia, hydrocele, hiccup, nasolacrimal duct blockade, physiologic phimosis and hymenal tags. For details, See Chapter 17 (Neonatology).

Later Infancy and Childhood

Tongue-tie (Ankyloglossia)

A true tongue-tie is characterized by a very short frenulum which may manifest as a prominent midline groove at the tip of the tongue as a result of traction and/or failure on the part of the child to lick his upper lip. This is not only infrequent, but also of not known functional significance. At worst, it may cause little dyslalia but never delayed speech. Only rarely it needs a surgical cut at 2–3 years of age. In practice, tongue-tie is an overdiagnosed condition.

Delayed Speech

Frequently, the parents are worried about some delay in intelligible speech even though the child is normal in all other ways including hearing. The child is in need of a greater **sensory stimulation**. Rather than talking to him in baby language and through gestures, they must spend more time in talking to him in clear speech. They need to be told that some normal children do take 3 years or longer to develop intelligible speech.

Eating Problem

Many otherwise normal and healthy-looking children (some may be rather thin), according to the parents, are fussy about their food habits. As a result, the mothers are always running after them with food bowls. They indulge in forcible feeding which is often resented by the child.

Such parents need to be told, after examination and certain limited investigations, that their “anxiety” about the child’s disinclination to eat is rather not well founded. They must forthwith stop forcible feeding or any kind of cajoling or bribing in which they may be indulging to make the child eat in accordance with their wishes.

Bedwetting

Bedwetting is not pathologic until the age of 5 years. The parents should be made to understand this physiologic fact and unnecessary interventions, including investigations, avoided.

Umbilical Hernia

A proportion of the babies (say 1 in 4) have umbilical hernia (1–5 cm diameter) in association with diastasis recti (divertication of abdominal recti muscles) as a result of imperfect closure or weakness of the umbilical ring. Most such hernias disappear by 1 year, practically all by 3–5 years of age. Strapping with a coin and a bandage is of no significance. Indications of surgery are as follows:

- Persistence beyond 3–5 years
- Rather than reduction, further increase in size after the age of 1 year
- Rarely, when it gets strangulated.

Protuberant Abdomen

A protuberant abdomen, the so-called **pot-belly**, is a normal finding in the neonates as well as between 6 months to 3 years of age despite absence of any abnormality. The parents need to be reassured about its normalcy.

Irregular/Asymmetrical Skull

Some otherwise normal babies have an asymmetrical head. If craniosynostosis is excluded, the parents should be advised to properly position the head. With this, it assumes proper rounding by 3–4 months age.

Bowlegs (*Genu Varum*)/Knock-knees (*Genu Valgum*)

Physiologic bowlegs (a wide space between knees when feet are placed close together) are a normal observation in the first 2 years of life. If all else is fine, it warrants no treatment. With the child's growth, during the third and fourth year, bowlegs are replaced by physiologic knock-knees which are more pronounced in obese children. Spontaneous improvement results during 4–10 years of age.

Flat Feet (*Pes Planovalgus*)

The flat feet, meaning increased area of ground contact with weight bearing because of imperfect longitudinal arch, are typically a common finding in normal children. It is normal for the arch to develop after toddler age. Physiologic flat foot, as a rule, is flexible. No treatment is needed.

HEAT INJURY

Exposure to excessive heat, raising the body temperature beyond the acceptable limits, may adversely affect the child in a number of ways.

- **Heat syncope** refers to a situation in which a child standing in the sun for prolonged periods becomes pale with fall in blood pressure and sudden collapse or fainting. It results from lack of blood supply to brain because of reduced return of blood to the heart as a consequence of vasodilatation and pooling of blood in the lower extremities. Interestingly, body temperature may not be raised. Response to shifting the child to a shady neighborhood and making him lie comfortably with his head slightly tilted down is gratifying. As a rule, he recovers in a matter of 5–10 minutes.
- **Heat cramps** manifested by painful and spasmodic contractions exercise in hot and humid environment due to excessive loss of sodium and chlorides from body.
- **Heat hyperpyrexia**, manifesting with body temperature of 106°F, is usually the result of disturbed heat regulating center or mechanism.
- **Heat stroke**, manifesting with as high a body temperature as 110°F, dry and hot skin delirium, seizures and significant change in sensorium, results from failure of temperature regulating mechanism leading to hyperpotassemia which may even prove fatal.

Treatment consists in lowering the body temperature by ice-water baths until it falls to 102°F. For heat injury in case of newborn, See Chapter 17 (Neonatology).

SHOCK

The term, **shock**, denotes a clinical state of poor perfusion to the extent that the body demands are not suitably met from a great increase in metabolic demands (oxygen consumption) and/or decrease in metabolic supply (oxygen delivery).

Types

Two major types are recognized—intravascular hypovolemia and intravascular normovolemia or hypervolemia.

1. **Intravascular hypovolemia** is caused by loss of volume in the form of loss of blood (severe hemorrhage), protein-rich fluid (nephrotic syndrome, burns), or protein-poor fluid (acute gastroenteritis), or decrease in vascular resistance (anaphylactic shock, drugs, denervation injuries and early warm septic shock).
2. **Intravascular normovolemia or hypervolemia** is caused by cardiac dysfunction (coronary artery disease, myocarditis, cardiomyopathy, hypoxemia, metabolic insult), inflow obstruction (pericardial tamponade, intracardiac tumors), outflow obstruction (malignant hypertension, congenital heart disease in the form of severe aortic stenosis or coarctation, or hypoplastic left heart syndrome) and arrhythmias (supraventricular tachycardia).

Clinical Features

These are by and large similar in the two types and include tachycardia, normal or low blood pressure, cool peripheral extremities due to profound vasoconstriction and hypoperfusion with the increasing severity of volume loss, there is tendency for the cooling to extent to the proximal parts. In shock due to loss of resistance, patients extremities are unduly warm due to vasodilatation. In addition, postural hypotension may be remarkable. An important example of this type of shock is septic shock associated with septicemia. As the vascular epithelium in this shock loses its integrity, it starts leaking fluid into the perivascular space, patient may develop adult respiratory distress syndrome (ARDS). With further progression, myocardial function decreases with reduced cardiac output together with secondary severe vasoconstriction. This is the stage of cold shock.

Diagnosis

It is based on a good history, physical examination and laboratory support. As the laboratory results are likely to take time, resuscitation of the patient with cardiorespiratory collapse and rest of the initial treatment must never be delayed, especially his oxygenation, ventilation and access to the vascular system through IV line or intraosseous line.

Among laboratory tests of special importance are or packed cell volume (PCV), serum calcium, glucose, potassium, urea-nitrogen, creatinine, liver function test (LFT), coagulation screen, blood culture, etc. Capillary refill time is a useful parameter of peripheral perfusion.

Swan-Ganz catheterization of pulmonary artery is of value to demonstrate a reduced cardiac output or index central venous pressure (CVP) and left atrial pressure (LAP) and very high systemic vascular resistance (SVR). Cardiac evaluation in nonvolumic shock should further include an echocardiography (ECG), a chest X-ray and ECG.

Treatment

Treatment of hypovolemic shock due to loss of intravascular of volume is replacement of volume which is

852 initially carried out by using isotonic solutions such as normal saline or lactated Ringer's solution. Whole blood, fresh frozen plasma or 5% albumin is administered in specific etiologic situations. Treatment of hypovolemic shock due to decrease in vascular resistance is volume resuscitation and administration of a vasoconstrictor.

Treatment of septic shock depends on its stage. In the initial warm stage, volume resuscitation and vasoconstrictors are needed. In the subsequent cold stage, therapy should include positive inotropes and afterload reduction. Broad-spectrum antibiotics are strongly recommended. Steroids are indicated only when Waterhouse-Friderichsen syndrome is suspected.

Treatment of normovolemic or hypovolemic shock due to myocardial failure is volume resuscitation, antiarrhythmic, inotropic and afterload-reducing agents, and correction of hypoxemia and metabolic abnormalities.

EMERGING AND RE-EMERGING INFECTIONS

Definitions

The term, **emerging infections**, denotes newly identified and previously unknown infections that cause public health problems either locally or globally.

The term, **re-emerging infections**, refer to reappearance of infections that had practically disappeared or previously minor infections that have assumed a public health magnitude, or known infections whose multidrug-resistant strains (MDRS) have appeared causing problems in effective treatment.

Classification

Box 48.2 gives a classification of emerging and re-emerging infections.

Noteworthy Emerging and Re-emerging Infections

Box 48.3 gives the list of emerging and re-emerging infections important in pediatric practice.

Contributing Factors

These are summarized in Box 48.4.

Control Measures

These include surveillance on outbreaks globally, newer vaccines as also vaccines with easier mode of administration,

Box 48.2

Classification of emerging and re-emerging infections

- Newly-recognized infectious diseases with identified or unidentified causative pathogen—AIDS, nipah virus disease
- Previously-recognized infectious disease with a newly identified causative pathogen—Whipple disease (microorganism *Tropheryma whippelii*)
- Previously known disease now identified as being of infectious origin—peptic ulcer disease (microorganism *Helicobacter pylori*)
- Known infectious diseases that are developing resistant strains—MDRS of typhoid fever, tuberculosis, *Staphylococcus*, *Streptococcus pneumoniae*.

Abbreviations: AIDS, acquired immunodeficiency syndrome; MDRS, multidrug-resistant strains.

Box 48.3

Important emerging and re-emerging infections

Emerging infections

- HIV
- SARS*
- Bird flu**
- *Helicobacter pylori*
- *Chlamydia pneumoniae*
- *Ehrlichia chaffeensis*
- *Legionella pneumophila*
- *Bartonella burgdoferi*
- MDRS
 - *Mycobacterium tuberculosis*
 - *Salmonella typhi*
 - *Staphylococcus aureus*
- *Enterococcus* species
- *Escherichia coli* 0157.H7
- *Vibrio cholera* 0139
- Hepatitis C
- Hepatitis E

Re-emerging infections

- *Leishmania donovani*
- Malaria
- Leptospirosis
- Plague
- Filariasis
- Dengue
- Japanese B encephalitis.

* Severe acute respiratory syndrome

** Avian influenza.

Abbreviation: MDRS, multidrug-resistant strains; HIV, human immunodeficiency virus.

Box 48.4

Factors contributing to emerging and re-emerging infections

- Advanced diagnostic modalities
- Behavioral and cultural changes
- Population growth shifts
- Sanitation
- Environmental changes
- Genetic changes
- Antibiotic resistance
- Immunosuppression
- Globalization
- Enhanced childcare facilities.

applied research, public health measures aimed at awareness and prevention, judicious use of antibiotics and MDR-resistant drugs.

EVIDENCE-BASED MEDICINE

Evidence-based medicine (EBM) may be defined as the process of systematically finding, apprising and using contemporaneous research findings as the basis for clinical decisions. In other words, it is the judicious use of current best evidence in making decisions about the care of individual patients. Thus, the systematically developed statements help in patient care in specific clinical circumstances. It is believed that such an approach makes clinical decision-making easy and improves quality of health care.

NEED FOR THE EVIDENCE-BASED MEDICINE

Certain changes in the health care scenario have brought about an increased accountability on the part of doctors.

- The increased access to medical information has increased patient awareness.
- The consumer protection act and similar movements in other countries where nonmedical persons can question the medical management has led to stress on accountability on part of clinicians.

Essential Steps in Evidence-based Medicine

- Identifying a clinical problem that needs a solution
- Finding the evidence
- Apprising the evidence for its credibility
- Applying it in clinical situations.

Sources of Evidence-based Medicine

These include:

- Systemic reviews such as Cochrane Database of Systematic Reviews
- Journals and software such as Journal of Evidence-based Health
- Websites such as Evidence-based Pediatrics University of Michigan (<https://www.med.umich.edu/pediatrics/ebm>)
- Organizations such as Cochrane Collaboration School of Health and Related Research (SchHARR).

Cochrane collaboration is the largest collection of evidence-based resources. It is named after Dr AL Cochrane who founded it in 1993, thereby pioneering the use of EBM. Its components are:

- Cochrane Database of Systematic Reviews
- Database of Abstracts of Reviews of Effectiveness (DARE)
- Cochrane Controlled Trials Register
- Cochrane Review Methodology Database
- Reviewers Handbook on the Science of Reviewing Research
- A Glossary of Methodological Terms and Cochrane Jargon.

Limitations of Evidence-based Medicine

- Evidence-based medicine practice needs new skills which are difficult to be developed by a busy practitioner
- It boosts the cost of health care
- Rather than taking advantage of clinician's experience and judgment, it promotes the so-called **cookbook medicine**
- Whether it has indeed helped in clinical circumstances remains unclear
- It fails to provide answers to all clinical controversies since evidence is based on primarily randomized controlled trials and systematic reviews.

Multiple Choice Questions

1. True observations about child adoption include each of the following, except:
 - A. Adoptive parents are responsible for child's care and welfare
 - B. Adoption from a couple's relatives is strongly recommended
 - C. The best way is through reputed adoptive agencies
 - D. As per law, the father cannot give his child in adoption without the consent of the mother
2. True observations about infantile tremor syndrome include each of the following, except:
 - A. A large majority of the cases are in 6–18 months age group
 - B. Anemia may be of any morphologic type, not necessarily megaloblastic
 - C. Tremors are most prominent in proximal parts of limbs
 - D. Zinc in therapeutic doses is strongly recommended
3. True observations about sudden infant death syndrome include each of the following, except:
 - A. Sudden unexpected death of an apparently healthy infant who had been put to bed without any suspicion of such an occurrence
 - B. Risk of a subsequent SIDS in the family is low
 - C. Etiology remains obscure
 - D. Parents need to be counseled on anticipatory guidance for future
4. Pick up the most appropriate observation:
 - A. Physiologic bowlegs is a normal finding in first 2 years of life
 - B. Bedwetting is not pathologic until the age of 5 years
 - C. True tongue-tie is infrequent
 - D. All of the above
5. Spot the wrong statement:
 - A. An umbilical hernia persisting beyond 6 months is an indication for surgery
 - B. Kveim test is of value in sarcoidosis
 - C. Sequela of histiocytosis include blindness and progressive pulmonary disease
 - D. Chronic fatigue syndrome is predominantly seen in adolescent girls in pediatric practice

Answers

1. B 2. C 3. B 4. D 5. A

Clinical Problem-solving

Review 1

A 16-year-old teenager presents with “tiredness all the time” and “not feeling like doing anything” for over a year. His school performance has taken a nosedive. He no longer goes for his evening skating and doesn’t socialize with friends. A couple of months prior to these complaints he had suffered from “flu”, taking some 2 weeks to recover from it. Physical examination essentially normal. All routine investigations (including ESR) are normal, except hemoglobin of 9.5 g/dL.

1. What is this teenager’s problem?
2. How to confirm the diagnosis?
3. How to treat such a patient?

Review 2

A 10-month-old infant, weighing 6.5 kg, is referred by a physician for status epileptics. Examination shows a plump-looking infant with tremors of the distal body parts and tremulous cry. Additionally, he has moderate pallor, light-colored sparse scalp hair and reticular pigmentation of knuckles. He no longer sits without support.

1. What is the most likely diagnosis?
2. What is the current view about its etiology?
3. How will you treat it?

Answers

Review 1

1. Chronic fatigue syndrome (CFS) in view of classical manifestations following an attack of flu and investigations essentially normal.
2. Diagnosis is by high index of suspicion and exclusion of differential diagnosis through investigations.
3. Emotional support for the patient and his parents with symptomatic therapy are the sheet-anchor of treatment of CFS.

Review 2

1. Infantile tremor syndrome in view of the classical presentation. On account of lack of familiarity about ITS, the referring physician made an error in diagnosing persistent tremors as “status epilepticus”.
2. Today it is believed to be a nutritional disorder, the precise role of different micronutrient deficiencies remaining unclear.
3. Treatment is primarily directed towards anemia and improvement in the nutritional status. Zinc in therapeutic doses is strongly recommended. Tremors may be controlled with phenobarbital, chlorpromazine, carbamazepine, propranolol, etc.

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

1. Dikshit AK. Nutritional dystrophy and anemia. *Indian J Child Health* 1957;6:132–136.
2. Gupte S. Infantile tremor syndrome Revisited. In: Gupte S (ed) *Recent Advances in Pediatrics (Special Vol. 18: Pediatric Neurology)*. New Delhi: Jaypee 2007:310–322.
3. Gupte S. Infantile tremor syndrome: A growing Asian problem, *Proceedings of 5th Intern Child Neurology Congress*, Tokyo 1990.
4. Jenson HB. Chronic fatigue syndrome. In: Kliegman RM, Stanton BF, St Geme II JW, Schor NF (eds): *Nelson Textbook of Pediatrics*, 20th edn. Philadelphia: Elsevier 2016:863–866.
5. Sharda B. Infantile tremor syndrome. In: Gupte S (ed). *Recent Advances in Pediatrics-3*. New Delhi: Jaypee 1993:55–66.

BOOK/MONOGRAPH

1. Henry EW. *Chronic fatigue Syndrome*, 3rd edn. Boston: Academic 2015.

SECTION 8

Pediatric Procedures

Section Outline

- 49. Pediatric Practical Procedures
- 50. Pediatric Laboratory Procedures

INTRODUCTION

Each and every pediatric scholar must learn the technique and develop skill in actually carrying out the frequently employed practical procedures, some therapeutic and others diagnostic, in pediatric practice. Most of these procedures can be performed bedside in addition to the procedure room.

GENERAL RULES/PRECAUTIONS

These are summarized in Box 49.1.

RESTRAINT AND POSITIONING

In order that a technical procedure is carried out successfully, particularly in infants, it is necessary to have the patient properly restrained and positioned. A struggling child will only lead to failure and disappointment.

Some centers may have the so-called *infant immobilization boards* which are quite useful. A commonly employed and a simple method of restraint, however, consists in mummifying the infant in a rectangular sheet. The infant is placed in the center of the sheet that is spread on a table. Only infant's head and neck should remain projecting beyond the upper border of the sheet. The infant's right arm is then straightened and adducted by the side of his trunk. The short edge of the sheet is passed in front of the arm, through the axilla and then behind the trunk. This end is then pulled and taken close to the short border of the sheet on infant's left side. The same procedure is repeated for the left arm. The edges

should be secured firmly with adhesive tape or safety-pins. An additional sheet may be wrapped around infant's legs to achieve still better restraint.

Remember to examine the digits for color, temperature and capillary pressure (indicating proper circulation) after restraining a limb. Also, make sure that cardiorespiratory function is not impaired.

INTRAMUSCULAR INJECTION

Usual Sites

- In infants and young children, anterolateral aspect of mid thigh.
- In older children, gluteal muscles are well developed, upper and outer quadrant of buttocks (gluteal region).
- In children and adolescents, mid-deltoid areas.

Method

- Hold the child securely to prevent movement of extremity.
- Thoroughly clean the skin with an antiseptic sponge, moving circularly from center outwardly.
- Hold skin taut and then insert the needle quickly.
- Check that needle is not in a blood vessel by a slight aspiration.
- Inject the material completely and then withdraw.

Special Note

- Size of needle varies (22–24 gauge size) with the viscosity of the drug being injected and the age of the child. It should not be more than 2.5 cm in length.
- In case of anterolateral aspect of thigh, needle should be inserted at an angle of 45°, pointing toward the knee.
- In case of gluteal region, the child should lie in prone position in the bed and the needle inserted perpendicular to the surface on which child is lying and not to his skin.
- Immediate massage and subsequent use of the muscle aids in absorption of the drug.
- Clean the area using appropriate agent (variable for different vaccines).
- Pinch up the skin with your fingers.
- Push a subcutaneous needle into the skin at an angle of about 60°.
- Draw on the plunger to check if the needle is not in a blood vessel.
- Administer the drug.
- Do not rub vigorously over the injection site.

Box 49.1

Vital general rules in pediatric practical procedures

- Before actually carrying out a procedure, salient features of the procedure should be explained to the attendants and to the grown-up child to ensure their cooperation.
- For all major procedures such as lumbar puncture, liver biopsy or bone marrow aspiration, it is obligatory to obtain a written and signed consent from the parents. All necessary equipments, including local anesthesia, requisite needles, containers, test tubes, syringes, etc. should be readily available near the procedure table to avoid last minute confusion and panick. The chamber in which the procedure is carried out should be well lit, tidy, noise-free and neither too cold nor too hot. The procedure should be performed under aseptic condition, including scrubbing and handwashing. A reasonable number of observers/assistants should be around to keep a check on the cardiorespiratory status as also for help in the procedure. Adequate positioning and restraint of the child during the procedure are vital for the successful outcome of the procedure.

858 INTRADERMAL INJECTION

This route is most often used for administering bacillus Calmette-Guerin (BCG) vaccine and tuberculin (Mantoux) test.

Method

- Clean the area of skin appropriately.
- Support child's arm with your nondominant hand and use finger to stretch the skin.
- Holding the syringe in your dominant hand almost flat on patient's skin, insert the needle into the skin with bevel of needle facing up, taking care that only the needle tip enters skin.
- Hold your nondominant thumb to hold the syringe close to skin while you inject the material.

Special Note

- Do not rub the site.
- After the injection, a clear flat raised wheal at the site should develop.

VENIPUNCTURE

For venipuncture, the choice is a visible vein in the antecubital fossa, back of the hand, dorsum of the foot or scalp. If not easily available, one may puncture the femoral, external jugular or internal jugular vein.

Femoral vein puncture consists in holding the hip fully abducted and the knee flexed to 90° and then palpating the femoral artery below the inguinal ligament (Fig. 49.1). The femoral vein is then entered by introducing the needle, perpendicular to the skin, just medially to the artery. The needle is allowed to pin the vein against the femur. After the needle has touched the bone, it is slowly withdrawn using negative pressure on the syringe. While this is being done, blood starts gushing into the syringe when the needle enters the lumen of the vein. After obtaining the blood, the needle is gently removed. Thereafter, firm and steady pressure should be applied over the vein for at least 2 minutes and preferably for 3–5 minutes.

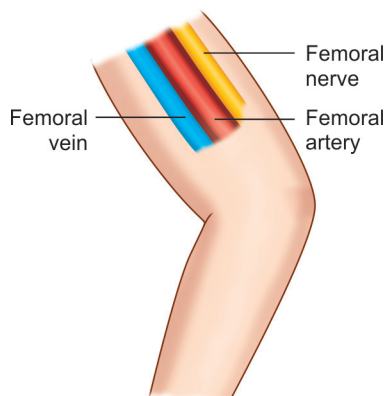


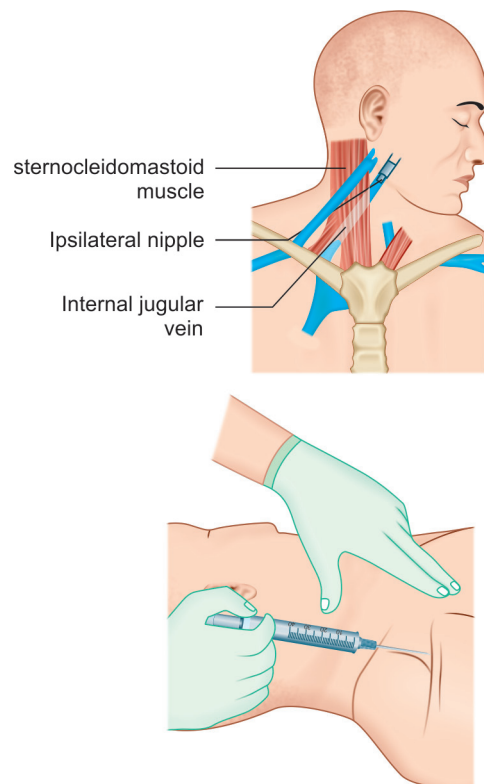
Fig. 49.1: Femoral vein puncture. Note that the vein lies medial to the artery.



Fig. 49.2: External jugular vein puncture. Position of the vein in the neck.

Femoral puncture is a risky procedure. Accidental puncture of the artery may cause hematoma, transient cyanosis or even ischemia and gangrene of the foot if the artery goes into prolonged spasm. Osteitis of the femur and arthritis of the hip may occur in occasional instances.

External jugular vein puncture consists in placing the child on a table in Trendelenburg position so that his shoulders are touching the table and the head is lying at a lower level than that of the trunk. The head is then turned through 90° to one side so that the external jugular vein is stretched and becomes visible crossing the sternomastoid muscle. At this point that the vein is punctured, especially when it gets distended while the child is crying. It is wise to exert pressure over the puncture side for 3–5 minutes after the needle has been withdrawn. For more clarity, See Figures 49.2 and 49.3.



Figs 49.3A and B: External jugular vein puncture. Practical details.

Internal jugular vein puncture is done by inserting the needle half way down the posterior border of the sternomastoid. The needle is directed beneath the muscle towards the suprasternal notch. The blood flows freely as the vein is entered, provided that a gentle but constant suction is maintained through the procedure. Sometimes, blood may be obtained only when the needle is being withdrawn. After removing the needle, firm pressure should be exerted over the puncture site for 3–5 minutes so as to reduce pressure in the vein. The child should be in his sitting position while this is done. The complications of the procedure include hematoma and damage to lungs (especially upper pleural space) and the trachea.

Collection of repeated blood samples, as in glucose tolerance test, may be done from a single venipuncture. A scalp vein needle is inserted in an antecubital or hand vein. A 2–3 ways stopcock is inserted into the catheter end. The dead space of the scalp vein catheter is filled with heparinized saline. When blood sample is required, the stopcock is removed and the solution filling catheter is withdrawn and discarded. A second syringe is then employed to obtain the desired quantity of blood. The catheter is again filled with heparinized saline solution and closed with stopcock until next sample is required. Remember that the samples obtained in this way are somewhat heparinized and are a source of plasma and not serum.

INTRAVENOUS (IV) INFUSION

In older children, an antecubital or wrist vein is usually good enough for intravenous infusion. Upto the age of 4 or 5 years, scalp vein infusion serves well. In a newborn, umbilical vein may be handy for exchange transfusion. As and when peripheral veins are not available in an emergency situation such as shock leading to collapsed peripheral veins, it may become necessary to use saphenous or femoral vein as such or by venesection

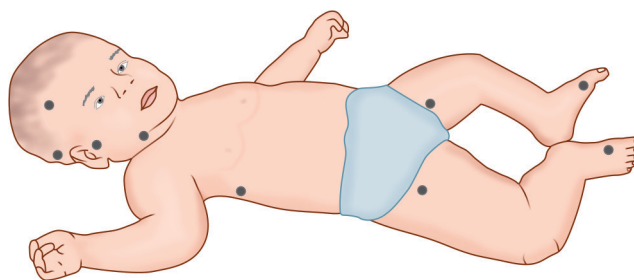


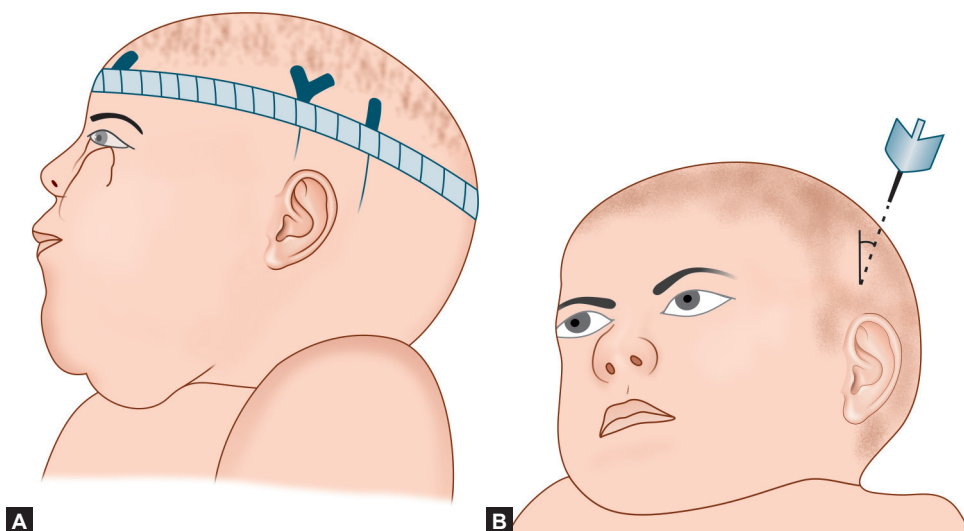
Fig. 49.4: Sites for intravenous infusion.

(cutdown or cutopen). Figure 49.4 highlights various sites for IV infusion.

Scalp Vein Infusion

Advantages of scalp vein infusion include rapidity of insertion, minimal trauma, steadiness and stability and preservation of veins for future needs. Its difficulty lies in as much as that it is essential to have the said area of scalp shaved which is often resented by the parents in India.

The veins most frequently employed are branches of temporal vein, posterior auricular vein and those on the forehead. When a suitable vein is detected, the hair over the area should be shaved. The skin is sterilized with iodine and spirit or ethanol. The vein is then distended by such stimuli as tapping it sharply with a finger and by obstructing the venous return by pressing a finger against a proximal segment (Fig. 49.5A). Once the vein is fixed by stretching the skin taut with fingers, the needle is made to pierce the skin beside the vein and inserted beneath the skin for a short distance before actually puncturing the vein. As the needle enters the vein, blood begins to flow into the polythene tubing. If the vein is collapsed, blood may not come in the tubing. A small quantity of saline is injected from the syringe into the tubing. If the needle is not in the vein, there appears a subcutaneous swelling. Once the needle is *in situ* (it is good to push it as far as possible into the vein), it should be fixed at an angle of 30° to the scalp with strips of adhesive plaster (Fig. 49.5B). It



Figs 49.5A and B: Scalp vein infusion. (A) Note the elastic band round the head. It acts as a tourniquet. The thumb may also be used to occlude the vein; (B) Note that the needle is *in situ*. It should be fixed with adhesive at an angle of 30° to the scalp.

860 is useful to tape a loop of the tubing, also to the adjacent scalp.

Now is the time to connect the scalp vein needle set to the drip set. In small infants, the gravity method of administering fluids from a bottle suspended at an elevation may fail because of the very small veins. In such instances, fluids may be administered slowly by a syringe.

Venesection (Cutdown or Cutopen)

In a seriously sick child, if fluids are urgently to be administered intravenously but no peripheral vein is available for venipuncture, cutdown may become necessary.

The recommended site is anterior to the medial malleolus where the internal saphenous vein runs. However, the same vein can be used at any site along its route.

The whole procedure should be done with full aseptic technique as in any surgery. After the leg is bound to padded splint in a position of external rotation, 1% procaine or xylocaine is infiltrated into the overlying skin of the prepared area. With a scalpel, a full thickness skin incision, 1 cm long, is made right angle to the vein. The incision is spread wide enough to expose the vein which is dissected free of fascia and subcutaneous fat. A careful observation about the flow of blood would confirm that it is a vein and not a tendon or nerve. A ligature is then tied distally round the vein to occlude venous return. Through a small incision on the upper surface of the vein, a polythene catheter is inserted for a distance of 2 cm up the vein. As the blood begins to flow, a second ligature just above the site of insertion is tied firmly round the vein and catheter to secure the latter in place. The catheter is then connected to the IV drip set gently, avoiding pulling and tearing the vein or withdrawal of the catheter from it.

The wound is then closed with fine stitches (just two are fair enough), which are removed in 3–4 days and covered with gauze and roller bandage. It is unwise to restrain the foot. That only boosts the risk of pressure sores and interference with circulation. Figure 49.6 shows the steps of venesection.

Umbilical Vein Catheterization (UVC)

Umbilical vein may come in handy for exchange transfusion during the first week of life or for IV infusion,

during this period of life, when other veins may not be available. The procedure consists of sterilization of the cord area and then cutting the cord 2 cm from the skin junction, i.e. close to the base of the stump. With the edge gripped with mosquito forceps, three blood vessels are seen at the base. Two are umbilical arteries with regular outline and thick wall. The umbilical vein has irregular outline and thin collapsed wall. After clearing the vein of any clot, etc. the catheter is advanced gently into its lumen for 5–7 cm. As soon as blood begins to flow freely into the catheter and then fills it completely, the catheter should be connected to the drip set or the syringe. At the end of the procedure, a sterile polyvinyl marker is required to be inserted in the orifice of the umbilical vein. It should be tied into facilitate a subsequent catheterization. Also, it is a wise policy to send the tip of the catheter for culture. It may be a potential source for septic embolization.

CENTRAL VENOUS ACCESS

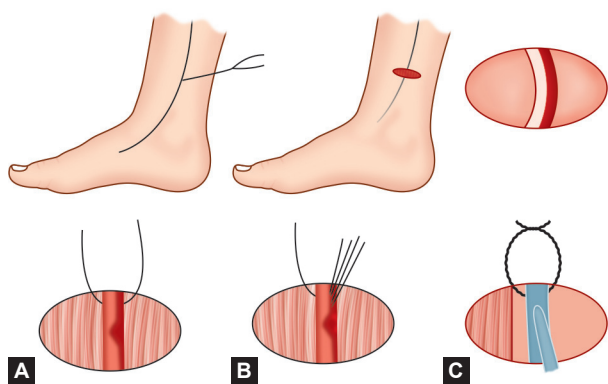
As and when peripheral line is not accessible or is not appropriate, central venous access devices (CVADs) are now used with greater frequency. CVADs include peripheral intravenous central catheters (PICCs), central venous catheters (CVCs), implantable access ports (IAPs), umbilical artery catheters (UACs), and umbilical vein catheters (UVCs). These devices can be placed in numerous sites, including the internal jugular vein (IJV), subclavian vein, femoral vein, peripheral veins leading to central access and other surgical access sites.

PICC lines have been used with great success in neonatal intensive care units (NICUs) and are considered a mainstay of vascular access in this setting. Although the lines are placed peripherally, usually in the antecubital or superficial saphenous vein, the distal tip remains in a large central vein. PICC lines are indicated in children who require intermediate term IV access for prolonged home or hospital therapy.

ARTERIAL PUNCTURE

It is particularly indicated for blood gas analysis and invasive blood pressure monitoring. The recommended sites are radial artery, branchial artery and temporal artery. The radial artery can be palpated in the center of the lateral third of the anterior aspect of wrist. Precisely speaking, it lies immediately lateral to the tendon of the muscle flexor carpi radialis. Branchial artery is the continuation of the axillary artery on the medial aspect of the arm and can be palpated with some difficulty. Temporal artery lies just anterior to the tragus of the ear. It is both palpable and visible once hair over the temporal region is shaved.

For the arterial puncture, the selected site is prepared aseptically, employing spirit, iodine and spirit in that order. A heparinized syringe with 21–23 gauge needle is employed for the puncture. In case of a radial puncture, the wrist is kept extended and the radial artery palpated and left hand fingers kept on it. Then, with the bevel



Figs 49.6A to C: Venesection. Note the steps.

facing upward, the needle is inserted little superior to the proximal skin crease inclined at an angle of 45° to the artery. At this stage, the needle should be gradually withdrawn as gentle suction is maintained. If blood fails to flow into the syringe, another attempt should be made by pushing the needle again in either direction without withdrawing it from the skin.

Once the sample of blood has been collected, the puncture site should be kept pressed for 5 minutes or more to safeguard against bleeding. The syringe (heparinized) containing blood sample is sealed and preserved in ice. It must be carried to the laboratory for immediate blood gas analysis. Since an arterial puncture is often painful and may cause hyperventilation, it may well be in order to employ a local anesthesia.

In case multiple samples of arterial blood are needed over a relatively shorter time, it is advisable to place an indwelling arterial line. Such a line would require to be continuously heparinized (1 unit/mL saline; 3–5 mL/hour) to safeguard against thrombosis. An alternative to arterial blood is arterialized capillary blood which may be obtained from a puncture over finger, heel or earlobe, provided that patient's tissue perfusion is good.

INTRAOSSEOUS INFUSION

In emergency situations when IV approach cannot be established, intraosseous may be ideal as a tideover temporary measure. Fracture, osteogenesis imperfecta, osteoporosis, cellulitis, infected burns, etc. are its contraindications.

The flat anteromedial surface of proximal tibia 1–2 cm below the tubercle, is the best site. Alternatively, distal tibia and distal femur may be employed (Fig. 49.7). The

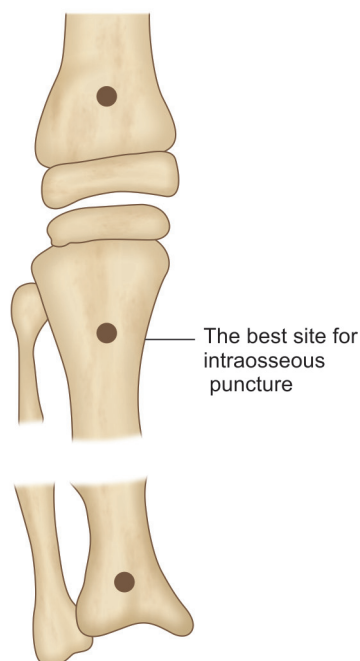


Fig. 49.7: Intraosseous infusion. Note the three sites recommended for insertion of the needle. Upper tibia is by and large the best site.

prepared part of the restrained leg is first injected with 861 local anesthesia. Then, a standard bone marrow needle or 14–18 gauge spinal needle is inserted perpendicularly to the skin. As soon as it reaches the periosteum, it is directed at a 60° angle inferiorly. Make sure that the bevel points away from the epiphyseal plate and the joint space. It is advanced further, using fair pressure. Arrival at the marrow is indicated by a loss of resistance. Usually, an insertion of the depth of 1 cm of the needle is sufficient for this purpose.

Once the needle is in the marrow, blood or marrow content can be freely aspirated by a saline-filled syringe. If a block of the needle with marrow contents is suspected, a couple of mL of saline may be infused slowly to remove the block. Once the free flow of blood is ensured, the needle is connected to a standard IV drip. As in an IV drip, interosseous infusion is run by gravity with the fluid bottle suspended 4–6 feet above the level of the patient. The procedure is fairly safe. Nevertheless, occasional complications include extravasation of fluid into subcutaneous tissues causing skin necrosis, local infection, cellulitis, osteomyelitis, epiphyseal insult causing tibial fracture and fat embolism. It must be reserved for emergency situations and as a short-term measure.

SUBCUTANEOUS INFUSION

The old regimen of subcutaneous infusion (hypodermoclysis) may be employed under very pressing circumstances when a vein cannot be entered and it is not possible to do a cutdown either. A drawback of this method is that it may cause remarkable shift in the body fluids. Also, it is difficult to give large amount of fluid by this route. The sites of choice are the subcutaneous tissues of axilla, upper back (interscapular area), thigh and flank.

A sterile fluid is run under the skin with a syringe or through a drip-set, using 20 gauge needle, until a tense swelling is produced and it is difficult to inject any more. Then an ampoule of hyaluronidase is injected straight into the needle or into the plastic tubing. This together with gentle massage diffuses the fluid into the tissues. By this technique 30–40 mL fluid/kg body weight can be injected at one sitting. Remember to avoid giving glucose saline over a long period by this method. It is advisable to restrict the method for only isotonic solutions.

INTRAPERITONEAL INFUSION

Though not a preferred method, blood and isotonic fluids may be administered by intraperitoneal route. A short bevelled needle is introduced through sterilized skin at the junction of upper one-third and lower two-third between the umbilicus and pubic symphysis. The drip set is connected to the needle. If the infusion starts running rapidly, the needle is in the peritoneal cavity. By this method, about 30 mL/kg body weight of fluid can be administered. An important precaution is that the bladder must be voided while performing this procedure.

862 RECTAL INFUSION

If a soft catheter is introduced into the rectum and then connected to drip-set, saline may be administered slowly at a rate of 30 ml/hour. The method is simple and can be carried out by nursing staff. It is, however, no match for the interosseous infusion as far as the reliability of the infusion in the presence of dehydration is concerned.

BONE MARROW ASPIRATION

For marrow puncture, the usual site and the method of choice for children is the iliac crest. In children less than 2 years of age, more so in the first 3 months of life, a point on the anteromedial aspect of tibia, about 2.5 cm below the tibial tubercle, is the recommended site. Sternal puncture is hardly required in children.

The procedure is carried out with full surgical precautions in a well-sedated child. The skin is infiltrated with 1% procaine or xylocaine upto the periosteum. With a rotating action, the marrow trocar and cannula are inserted through the skin down to the periosteum and then through the cortex into the marrow cavity. As soon as the needle enters the cavity, some give is felt and there is sudden lack of resistance. With the needle firmly fixed *in situ*, trocar is removed. A fleck of marrow on the tip of the trocar confirms that the needle is in the marrow cavity.

The time is now ripe for fitting a dry 20 mL syringe to the needle. With strong suction for a few seconds, about 0.2 mL of marrow is aspirated into the syringe. After the aspiration, trocar is replaced and the needle withdrawn. The puncture site is pressed with a finger for 3–5 minutes. A sterile dry dressing is applied over the site. The aspirate is smeared in equal amounts on 8–10 clean glass slides which are waved in the air to accomplish fast drying.

BONE MARROW TREPINE

The child is placed in lumbar puncture (LP) position. At the lower end of the iliac crest, posterior superior iliac supine is located. The point for puncture is 1 cm above the spine in a young child and 2 cm above it in an older one (as in the case marrow aspiration).

After local anesthesia, the skin is incised with a sharp scalpel. The stylet of the Tamhidi-Swain trephine needle is locked and the handle inserted through the incision so that it touches the iliac crest. With steady pressure, it is rotated clockwise and anticlockwise down into the bone. As it cuts into the bone, making the operator feel the give, the stylet is removed. The needle is then little withdrawn and pushed about 2.5 cm in a different direction. This breaks the bone specimen at the distal edge of the needle. After gently removing the needle, the chip of bone is extruded from it into a suitable histologic fixative.

LUMBAR PUNCTURE

This procedure is best avoided in the presence of papilledema in which case herniation of the medullary cone may prove dangerous. In local diseases of the lumbar spine and skin sepsis also, it is advisable not to do it.

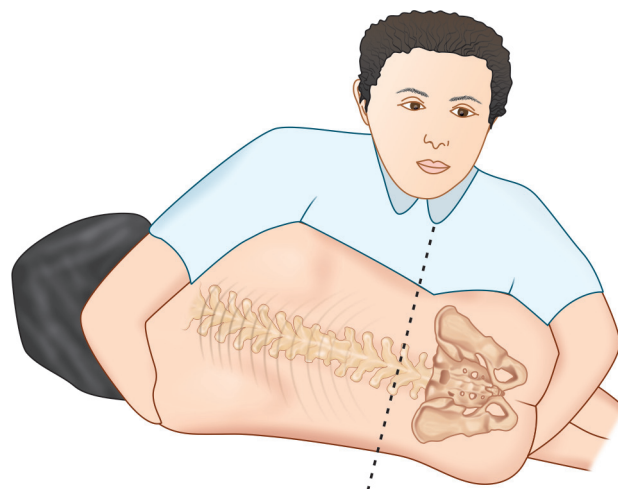


Fig. 49.8: Lumbar puncture. Lateral recumbent position.

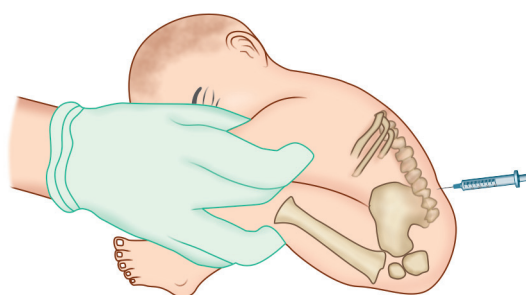


Fig. 49.9: Lumbar puncture. Puncture method.

The child is restrained either in lateral recumbant position with the neck flexed to the chest and the knees drawn to the abdomen, or in a sitting position. An imaginary line joining the two iliac crests passes through the 4th lumbar vertebra. A space above (3rd intervertebral space) or below (4th intervertebral space) this line may be chosen as the site of the LP (Figs 49.8 and 49.9).

The chosen site is prepared aseptically and then preferably infiltrated with 1% procaine, even in neonates. The LP needle with stylet in position is introduced into the said space, pointing somewhat towards the head. As the needle pierces the dura, a distinct give is felt. At this point, stylet may be withdrawn to watch for the fluid. The latter is collected in sterile vials. At the beginning and end of collection, the pressure may be measured employing a 3 way stopcock and manometer. After this, the stylet is replaced and the needle is withdrawn. The puncture site is sealed with tincture benzoin.

The details of cerebrospinal fluid (CSF) examination are given in Chapter 44 (Pediatric Ear, Nose and Throat (ENT) Problems).

SUBDURAL PUNCTURE OR TAP

Though not as safe as LP, it is indeed indicated when subdural effusion or hematoma is suspected. The well-sedated child is restrained adequately, the head being held by the nurse. The shaved scalp in the region of the anterior fontanel is prepared aseptically. A fine bevelled needle with stylet is employed to puncture the lateral angle of the fontanel. It should enter at an angle of 90° to the scalp.

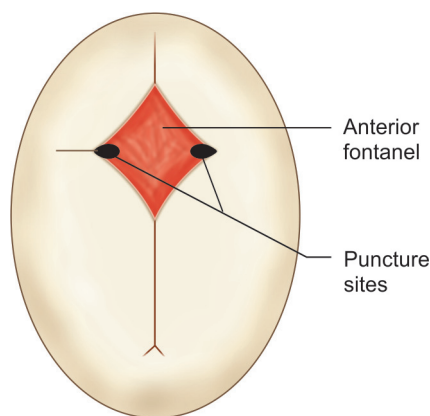


Fig. 49.10: Subdural tap. Note the two sites of puncture. The procedure must always be done on the other side but with a separate needle. No suction with the syringe must ever be applied.

The operator feels a give as the needle pierces the dura. At this point the stylet is withdrawn. The subdural fluid flows out as proteinaceous, cloudy, yellow, brown or red material. It is collected in sterile vials, remembering that not more than 10–15 mL of it is to be removed per side at one sitting. After the needle is withdrawn, firm pressure is exerted with a cotton wool ball. The puncture is sealed with tincture benzoin.

The procedure is always to be repeated on the opposite side, irrespective whether the first tap is negative or positive (Fig. 49.10). The subdural fluid is subjected to usual laboratory investigations. Its protein content should be at least 40 mg% more than that of CSF obtained by LP.

A frequent observation, after the tap some leakage of the fluid occurs under the scalp, leading to false positive transillumination. Its complications include hemorrhage, persisting effusion and infrequently, porencephaly, if the brain is punctured.

VENTRICULAR TAP

Its technique is more or less the same as that of subdural tap. Here the needle is, however, much longer (Fig. 49.11). Secondly, it is required to be advanced towards the inner canthus of the ipsilateral eye and not 90° (perpendicular) to the skull.

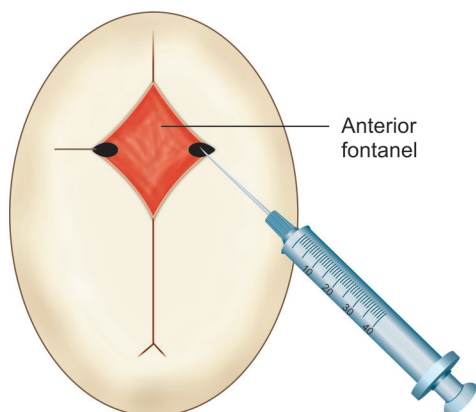


Fig. 49.11: Ventricular tap. A relatively longer needle must be advanced forwards and inwards towards the inner canthus on the same side. Suction with the syringe is contraindicated.

THORACENTESIS

The procedure is employed to remove pleural fluid or air (both for diagnostic and therapeutic purposes), to induce pneumothorax or to inject antibiotics in cases of empyema. In order to know the exact position of effusion, an X-ray chest should always be done before undertaking thoracentesis.

The chosen area (8th or 9th intercostal space in the posterior axillary line or the area of maximum dullness) is prepared aseptically while the child sits back on the bed and leans forward against a stool, bed, stand or chair back. The area is infiltrated with 1% procaine down to the pleura.

A large-bore needle with a syringe is inserted in the space along the upper edge of the lower rib. This is important to avoid injury to the intercostal nerves and blood vessels. Entry into the pleural cavity is indicated by a feeling of give. With suction, the fluid begins to flow into the syringe. Not more than 100–500 mL should be removed at a time. Since the risk of introducing air (pneumothorax) is considerable, it is advisable to employ a 3 way stopcock between the needle and the syringe. When the needle is withdrawn, the skin puncture should be sealed with tincture benzoin.

PERICARDIAL PUNCTURE

The procedure is indicated in suspected pericardial effusion and for relieving cardiac embarrassment in cardiac tamponade due to collection of large amount of fluid or blood.

The child is made to sit at 60° angle. The chosen site (5th left intercostal space, 1–2 cm within the left outer border to the cardiac dullness, or just outside the apex) is prepared aseptically and then infiltrated with 1% procaine. A large bore needle, connected to a 3 way stopcock and 50 mL syringe, is inserted into the intercostal space at the upper border of the rib. The direction of the needle should be posterior and towards the spine. As soon as the needle edge is in the pericardial space, fluid begins to come on aspiration.

ABDOMINAL PARACENTESIS

After voiding, the patient lies in semi-sitting position in the bed or on a table. The skin below the umbilicus is prepared aseptically and 1% procaine infiltrated at the site of puncture, usually midway between the umbilicus and pubic symphysis (in the lower quadrant or in the midline). A largebore needle or trocar is then pushed into the abdominal cavity. Its direction should be rather oblique so that leakage of fluid may be prevented. After sufficient fluid is aspirated, the puncture site is sealed with tincture benzoin to prevent oozing.

SUPRAPUBIC BLADDER ASPIRATION

When collection of urine without contamination becomes difficult in infants and young children, this procedure comes in hand.

864 **Method**

- Make sure that bladder is full, i.e it should be palpably enlarged above pubis.
- Sterile the overlying skin carefully.
- Place the infant in a supine position on a flat surface with proper restraint in frog-leg position.
- Firmly and swiftly, introduce a 21–22 gauge size needle attached to a syringe at a point 1–2 cm above pubis with needle, almost perpendicular to skin with a slight tilt (about 10°) downward.
- As the bladder is penetrated, change in resistance to the needle movement is felt.
- At this stage, aspirate the urine applying light pressure on the syringe.
- After urine has been collected, withdraw the needle with a single swift motion and apply pressure over the spot for some time.

HEEL PUNCTURE

It is useful for collecting capillary blood sample in neonates and young children for various hematologic, biochemical and blood gas analysis.

Method

- Heel is warmed by applying a warm towel to it for 5 minutes.
- Puncture the area (most medial or lateral aspect) with a needle perpendicular to the surface, the puncture not exceeding 2.5 mm depth.
- First drop of blood is wiped off and subsequent flow is collected in a capillary tube.

Special Note

Heel should never be milked to increase sample over flow.

LIVER BIOPSY

Liver biopsy may provide valuable information in primary diseases of the liver such as Indian childhood cirrhosis, other cirrhosis, hepatitis, unexplained hepatomegaly as well as diseases like tuberculosis in which liver involvement may be secondary. Before doing a liver biopsy, it is important to ensure that the prothrombin time of the patient is within normal limits.

The blood group should also be ascertained. In the presence of a bleeding diathesis, the procedure is best not done. The well-sedated child is made to lie on the edge of the table with his hands kept behind the head. In the midaxillary line, at the level of the tenth intercostal space, local anesthesia is infiltrated after proper cleansing of the skin with iodine and spirit. The liver biopsy needle (Tru-cut needle or Vim-Silverman needle) with the stylet is inserted through the ninth or tenth space or through subcostal approach into the liver tissue (Fig. 49.12). Then the stylet is withdrawn and the split portion is pushed inside the hollow needle. It is advanced further into the liver. At this stage, the outer needle too is advanced into the liver fully. Thereafter,

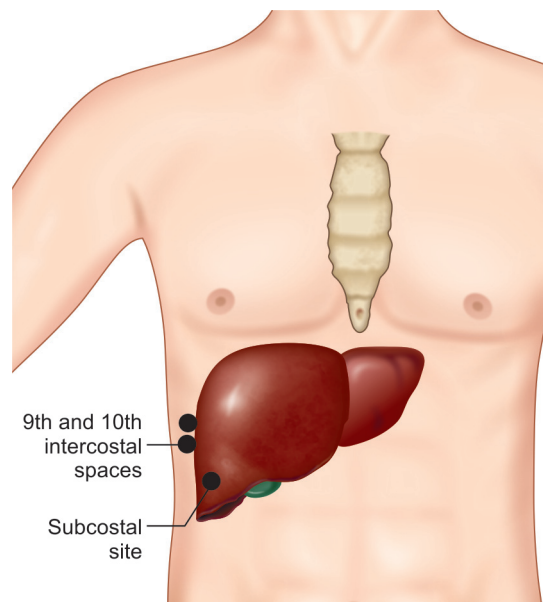


Fig. 49.12: Liver biopsy. Note the sites.

the whole needle is rotated through a full circle. This breaks the liver chip (that is attached to the needle) from the rest of the liver. The entire apparatus is withdrawn. The skin wound is sealed with tincture benzoin and the child watched for the next 24 hours. Alternatively, one may use the Menghini needle. The advantages of this needle include:

- No rotation of the needle is required
- The procedure takes less time (just half a minute).

KIDNEY BIOPSY

Kidney biopsy is of value in evaluation of cases of nephrotic syndrome not responsive to usual therapy with corticosteroids, progressive renal failure of obscure cause, undiagnosed hematuria, and conditions such as systemic lupus erythematosus (SLE). For evaluation of response to therapy and prognosis of the disease, periodic biopsies are of greater value.

Every child fixed for kidney biopsy must have a plain X-ray abdomen, ultrasound, and an intravenous pyelogram (IVP) for ascertaining the position and the size of the kidneys prior to the procedure. It is dangerous to conduct this procedure in the presence of a bleeding diathesis, polycystic disease, solitary kidney, severe systemic hypertension, hydronephrosis and tumors of kidney or adrenal. Following an adequate sedation, the child is made to lie prone with head turned to a side, arms abducted and forearms by the side of the head. A pillow or a rolled-up towel is placed under his abdomen.

The usual site for biopsy is 2 cm below and medial to the tip of the 12th rib (lower border). After the aseptic preparation of the site, 1% procaine is infiltrated locally. Then, a 20 gauge long needle (about 8 cm) is inserted gradually in a sagittal plane parallel to the spine until it hits the kidney. The later moves up and down with respiration, provided that it is in. The depth to which it has entered is marked and it is withdrawn. The track is anesthetized.

Then, Tru-cut or Vim-Silverman needle with stylet is introduced along the anesthetized tract, while the patients takes deep breath, till it pierces the kidney capsule. The position is confirmed by to and fro movement of the needle with respiration. The stylet is removed and the forked cutting needle is inserted to its full length. The patient is asked to hold breath and the outer needle is pushed deeper so that it covers fully the forked needle. The whole apparatus is now rotated a full circle (360°), leading to cutting of the biopsy material from the kidney. Finally, the apparatus is withdrawn and the puncture site sealed with tincture benzoin. The child is kept in supine position and observed for 24 hours. He should be encouraged to take enough of fluids and normal diet after he is out of the sedation. If carefully done by an expert, kidney biopsy is a fairly safe procedure. Microscopic hematuria is usually seen in a large majority of the cases. It is transient and disappears in 2–3 days. Massive hemorrhage, pain abdomen, hematoma, intrarenal arteriovenous fistula, etc. may occasionally complicate the procedure.

INTUBATION

For technique of passing the tube into the stomach and tube feeding, See Chapter 12 (Infant and Young Child Feeding).

For the purpose of obtaining gastric aspirate (lavage) for acid-fast bacillus (AFB), the child needs to be fasted overnight. When he wakes up in the morning, a 10 mL syringe is employed to aspirate all the gastric contents. The lavage thus obtained is collected into a sterile bottle. Then, 10 mL of distilled water is instilled into the stomach which is washed by frequent movements of syringe piston. The washing is aspirated and shifted to the same bottle. The material is sent to the laboratory for AFB (both direct smear and culture).

ENDOTRACHEAL INTUBATION

Refer Chapters 17 (Neonatology) and 44 (Pediatrics Ear, Nose and Throat {ENT} Problems).

PHOTOTHERAPY

Refer Chapter 17 (Neonatology).

EXCHANGE TRANSFUSION

Exchange transfusion is a potentially life-saving procedure that is done to counteract the effects of serious jaundice or changes in the blood due to diseases such as sickle cell anemia. The procedure involves slowly removing the patient's blood and replacing it with fresh donor blood or plasma.

An exchange transfusion requires that the patient's blood be removed and replaced. In most cases, this involves placing one or more thin tubes, called catheters, into a blood vessel. The exchange transfusion is done in cycles, each one usually lasts a few minutes.

In conditions such as neonatal polycythemia, a specific amount of the child's blood is removed and replaced with a normal saline solution, plasma (the clear liquid part of blood), or albumin (a solution of blood proteins). This decreases the total number of red blood cells in the body and makes it easier for blood to flow through the body.

Why the Procedure is Performed?

An exchange transfusion may be needed to treat the following conditions:

- Dangerously high red blood cell count in a newborn (neonatal polycythemia).
- Rh-induced hemolytic disease of the newborn.
- Severe disturbances in body chemistry.
- Severe newborn jaundice that does not respond to phototherapy with bili lights.
- Severe sickle cell crisis.
- Toxic effects of certain drugs.

For double-volume exchange transfusions for hemolytic disease of the newborn or for hyperbilirubinemia without hemolysis, the blood used will be packed cells (type O, Rh specific for the infant) resuspended to the desired hematocrit in compatible fresh frozen plasma.

A partial exchange transfusion is often done for polycythemia (See section on polycythemia). Although the standard anticoagulant citrate phosphate dextrose solution (CPD) is acidic, the blood need not be buffered. If the infant is severely acidemic, consult the staff neonatologist. If possible, the infant should be nil per os (NPO) and the stomach contents aspirated prior to the procedure. The exchange transfusion should be done under a radiant warmer using sterile technique. The donor blood should be warmed using the blood warmer to a temperature not exceeding 37°C. The infants blood pressure, respiratory rate, heart rate and general condition should be monitored during the exchange transfusion according to standard nursing protocol.

If the serum bilirubin concentration is at a dangerous level and the blood for exchange transfusion is not yet ready, consider priming the infant with 1 gram/kg (4 mL/kg) of a 25% solution of salt-poor albumin to bind additional bilirubin and keep it in the circulation until the exchange can be accomplished.

The umbilical vein catheter should be inserted until there is free flow of blood immediately prior to starting the exchange transfusion. See section on placement of umbilical catheters for technique. The exchange transfusion should not be done through an umbilical artery line unless the umbilical artery catheter (UAC) is used only for blood withdrawal with simultaneous replacement through the umbilical vein or peripheral IV. At the beginning of the exchange transfusion, the first blood sample withdrawn should be sent for:

- Total and direct bilirubin
- Hemoglobin and hematocrit
- Glucose and
- Calcium.

866 Use the **exchange transfusion kit**, which contains catheters, stopcocks, waste bag, and calcium gluconate. Ideally, blood (or colloid in the event of a partial volume exchange) should be infused through a peripheral vein at a rate equal to blood withdrawal from the umbilical vein catheters (UVC). If the **push-pull** (single catheter) technique is utilized, no more than 5 mL/kg body weight should be withdrawn at one time. The exchange volume is generally twice the infant's blood volume (generally estimated to be 80 mL/kg). The total volume exchange should not exceed one adult unit of blood (450–500 mL). A standard two-volume exchange will remove approximately 85% of the red cells in circulation before the exchange and reduce the serum indirect bilirubin level by one-half. The exchange of blood should require a minimum of 45 minutes.

The need for giving supplemental calcium is controversial. If used give 0.5–1.0 mL of 10% calcium gluconate IV, after each 100 mL of exchange blood. Monitor heart rate for bradycardia. At the end of an exchange transfusion blood should be sent for sodium, glucose, calcium, total and direct bilirubin, and hemoglobin and hematocrit. At the end of an exchange transfusion, the UVC is usually removed. In the event of a subsequent exchange, a new catheter can be inserted. Hypoglycemia often occurs in the first or second hour, following an exchange transfusion. It is therefore necessary to monitor blood glucose levels for the first several hours after exchange.

The serum bilirubin concentration rebounds to a value approximately halfway between the pre and post-exchange levels by two hours after completing the exchange transfusion. Therefore, the serum bilirubin concentration should be monitored at 2–4 hours after exchange and subsequently every 3–4 hours. Feedings may be attempted 2–4 hours after the exchange transfusion.

Risks

General risks are the same as with any transfusion. Other possible complications include:

- Blood clots.
- Changes in blood chemistry (high or low potassium, low calcium, low glucose, change in acid-base balance in the blood).
- Heart and lung problems.
- Infection (very low risk due to careful screening of blood).
- Shock, if not enough blood is replaced.

The infant may need to be monitored for several days in the hospital after the transfusion. The length of stay depends on what condition the exchange transfusion was performed to treat.

LYMPH NODE BIOPSY

After making the skin incision directly over the lymph node proposed to be biopsied in line with the natural skin creases, blunt dissection should be done all around and under the node so that it is completely free. Then, the capsule is held with a forceps, making sure that the node

itself is in no way held and traumatized and removed. After the lymph node is removed, it is cut in half. The cut section is inspected. Then the pieces are placed in formalin and transported to the pathology laboratory.

FINE NEEDLE ASPIRATION

Being minimally invasive, requiring no sedation. It is very useful for cytological and bacteriological examination of a mass or a lymph node. It aids in tissue diagnosis and in determining what the course of management should be.

Requirements

- 2.5–4 cm (20–25 gauge) needle (a small-bore needle causes less shearing force on tissues but obtain a very small sample).
- 10–20 mL plastic disposable syringe.
- Clean glass slides.
- 70–90% ethanol for routine wet fixation.
- Containers with specific culture media whenever required.

Method

- Sterilize the site.
- Local anesthesia, though usually not required, may be employed in anxious children.
- Immobilize the lump or the skin over the area to be biopsied between your thumb and finger with one hand.
- Hold the syringe on the other hand and insert needle into assigned area, perpendicular to skin surface and position the needle within target tissues.
- Pull the syringe plunger to apply negative pressure.
- As pressure is maintained, make several punctures through the lump.
- Release the negative pressure.
- While needle remains in target tissue, withdraw the needle.
- Detach the needle, clear some air, 2–3 mL into syringe.
- Reattach the needle and blow aspirate on to the slide.

Special Role

As the sample tissue is very small, it gets suck into syringe lumen and is hard to remove. So, you may need to repeat the procedure. Deep biopsies can be obtained with the assistance of radiologic and imaging techniques such as ultrasonography.

Caution

The following factors may contribute to an unsatisfactory yield during fine needle aspiration cytology (FNAC):

- When the needle misses the lesion tangentially.
- When the central area is cystic/necrotic/ hemorrhagic and devoid of diagnostic material.
- When there is a small malignant lesion close to a dominant benign mass.
- When the target tissue is fibrosclerotic and poor in cells.

GASTRIC LAVAGE

It is a very useful procedure in accidental poisoning (except corrosives and hydrocarbons), in managing upper gastrointestinal bleeding and for collecting samples of gastric juice for diagnosis of AFB.

Method

- Have all the equipment ready (Ryle's tube, suction apparatus, liquid paraffin mouth gag and saline).
- Place the child supine with head hyperextended and supported underneath by a hand.
- Open the mouth and use the mouth gag.
- After lubricating the tube with liquid paraffin (avoid it in a neonate), advance the tube over the tongue towards the back of throat. Keep advancing the tube until the mark on the tube reaches the tip. Make sure tube has not entered trachea. Passage into trachea causes sudden apnea and obstruction to insertion of tube.
- Confirm that tube is in the stomach by pushing air through the tube and auscultating over stomach. Bubbling of air when the outer end is placed in a cup of water indicates that tube is in trachea rather than stomach.
- Fix the tube securely on the face with adhesive tape.
- Gently suction out the gastric contents. Perform lavage of stomach using aliquots of normal saline (10–100 ml/kg/cycle). Keep repeating the cycle till the color of the returning fluid is the same as the lavage fluid.
- While removing the tube, always pinch its end to prevent spilling of the contents into trachea.

Special Note

- The tube may well be inserted through the nostril.
- Do not use excessive force while passing the tube.
- Watch out for laryngospasm and bradycardia during the procedure.

MANUAL REMOVAL OF FOREIGN BODY FROM AIRWAY

Foreign body should be seriously suspected in case of spontaneous respiratory distress associated with coughing, gagging, stridor, cyanosis or wheezing. Do not try to remove it by finger sweep which may push it back and deep into the airway.

Removal in an Infant

Back Blow Chest Thrust

- Hold the infant face down on your forearm which in turn should rest on your thigh.
- Support head of your hand between the shoulder blades of the infant.
- Now turn the infant around as a unit to a supine position while firmly supporting the head and neck. Administer up to 5 quick chest thrusts in a similar method and location as used for chest compression.
- The whole process may be repeated until the foreign body is expelled out.

Removal in a Child Older than 1 Year

Subdiaphragmatic Abdominal Thrusts (Heimlich's Maneuver)

It increases the intrathoracic pressure and creates an artificial bout of cough which forces foreign body out of the airway. This maneuver is not employed in infants because of the risk of liver injury.

Heimlich's Maneuver in Conscious Child

- Stand behind the child and encircle his torso by putting both arms directly under his axillae.
- Place the thumb side of one fist against the child's abdomen in midline, slightly above the naval and well below xiphoid. With the other hand, grasp the first and exert quick upward thrust taking care not to touch the xiphoid process or lower rib margin.
- Each thrust should be forceful enough and intended to relieve obstruction.

Heimlich's Maneuver in Unconscious Child

- Position the child in a supine position and kneel at his feet.
- Place the heel of one hand on child's abdomen in the midline, slightly above the naval and well below the rib cage.
- Place the second hand on top of the first and press into the abdomen with quick upward thrust.

CARDIAC RESUSCITATION

As soon as cardiac arrest is suspected, the following steps should be taken:

- At once, clear the airway and administer mouth-to-mouth breathing for as long as necessary.
- For closed cardiac massage, while the patient is supine on a firm surface such as a table or floor, place the heel of the hand over the lower part of the sternum. Press down firmly so as to depress the sternum by 1–5 cm. This needs to be repeated very fast, 90–120 times per minute. Palpability of a good femoral pulse is a reasonable sign of the adequacy of the force applied for the massage.
- Check the size of the pupils from time to time. Good response to light is a sensitive indicator of the adequacy of the massage.
- If, in spite of, a good external cardiac massage, the patient fails to be resuscitated, obtain an electrocardiogram (ECG), and resort to measures such as improvement in oxygenation, replacement of blood volume deficit, intracardiac adrenaline, calcium or bicarbonate.
- A fibrillating patient can often be made to have normal rhythm by employing an external defibrillator. Finally, it may be clarified that the ultimate outcome of cardiac arrest depends on the etiologic factors(s). However, increasing number of infants and children can be successfully resuscitated if external cardiac massage is begun immediately on detection.

Table 49.1: Etiology of respiratory failure needing ventilatory support

System	Neonates	Infants and children
Pulmonary	RDS, bronchopulmonary dysplasia, meconium aspiration, bronchopneumonia, pulmonary hemorrhage, congenital malformations	FB, epiglottitis, diphtheria croup, angioneurotic edema, pneumonia, bronchiolitis, severe acute asthma, near-drowning, shock lung
Cardiovascular	CCF, cardiac arrest, shock, PDA	CCF, cardiac arrest, shock, post-cardiac surgery
Neurologic	HIE, severe apneic attacks, IVH, congenital polio, heavy maternal sedation, myopathy (WH disease)	Acute polio, GB syndrome, CNS infections, head injury, status epilepticus, ICSOL, uncal herniation

Abbreviations: RDS, respiratory distress syndrome; CCF, congestive cardiac failure; PDA, patent ductus arteriosus; HIE, hypoxic-ischemic encephalopathy; IVH, intraventricular hemorrhage; WH disease, Wolf-Hirschhorn syndrome; GBS, Guillain-Barré syndrome; ICSOL, intracranial space-occupying lesion; FB, foreign body.

ASSISTED VENTILATION

The term, **assisted ventilation**, implies mechanical provision of oxygenation of circulation in order to maintain the gaseous concentration and pH of blood at an optimal level in the event of respiratory failure (Table 49.1).

A ventilator is defined as a mechanical device for providing artificial ventilation of the lungs. It may be hand-operated or machine-driven. The machine-driven ventilator may be automatic and very sophisticated as regards its ability to control and monitor flow of air to the lungs. Ventilation may be of two types:

1. **Intermittent positive pressure** in which pulmonary ventilation is provided by administering oxygen for the inflation of lungs under positive pressure.
2. **Continuous positive pressure** in which pulmonary ventilation is provided by administering oxygen for inflation of the lungs under a continuous positive pressure that is never allowed to return to zero.

Bag and Mask Ventilation

This life-saving procedure usually employs self-inflating Ambu bag and is capable of delivering 90% oxygen, if a corrugated tube is attached to the bag as a reservoir. This kind of ventilation is most suitable for resuscitating an asphyxiated/apneic neonate Chapter 17 (Neonatology) in spite of reasonable suctioning, clearing of the airway plus tactile stimulation.

Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) consists in providing a continuous supply of humidified oxygen-air mixture. The patient exhales against a water column kept at a level to maintain the required pressure resistance in relation to the magnitude of the positive end-expiratory pressure (PEEP) that is aimed at. It may be administered by a tight-fitting face mask, nasal prongs, nasopharyngeal catheter or endotracheal tube. CPAP is of particular benefit in respiratory distress syndrome (RDS), hyaline membrane disease (HMD), inflammatory disorders, atelectasis, etc.

Mechanical Ventilation

When 100% oxygen or CPAP fails to revert apnea or acute respiratory failure, mechanical ventilation is indicated so that arterial pH and blood gases are maintained at the optimal level, i.e. within normal range. It is best suited in

acute respiratory failure accompanying polio, Guillain-Barré syndrome, tetanus, accidental poisoning or other self-limited neurologic conditions.

Mechanical ventilation invariably needs intubation of the trachea. Some° of hypercarbia and hypoxemia is quite acceptable if oxygen-induced or stretch-induced injury to lung is to be avoided. Moderate hypercarbia with PCO₂ 60–80 mmHg and moderate hypoxemia with oxygen saturation 85–95% are well tolerated. It is, as a rule, started with conventional volume driven ventilators. If conventional ventilators fail to bring about improvement in oxygenation, high frequency jet or oscillator ventilators are used as rescue therapy.

Monitoring of ventilation by clinical and investigative measures is vital. In adequate ventilation, the subject shows pink color, adequate air entry and chest expansion with absence of retraction, prompt capillary filling in just 2 seconds or less and normal blood pressure (BP). Pulse oximetry indicates oxygen saturation of 90–95%. Blood gas analyses shows paO₂ 60–90 mm Hg, PaCO₂ 40–45 mm Hg and even up to 60 mmHg₂ in chronic situation, and pH 7.35–7.45.

During ventilation, a supportive care of high magnitude is warranted to ensure fluid and electrolyte homeostasis, thermoneutral environment and optimal functioning of cardiovascular system (CVS). Fluids are, as a rule, restricted since there is little insensible loss and high incidence of inappropriate secretion of antidiuretic hormone (ADH). Weaning from the ventilator is guided by the clinical status, natural history of the underlying condition and status of blood gases, and is carried out in a set manner, stepping down the settings of the ventilator by increments. Before extubation, he is attached to CPAP mode and placed in oxygen hood. Complications of ventilation are related to intubation, or barotrauma (Table 49.2).

Refractory life-threatening respiratory failure (not responsive to mechanical ventilation) is an indication for extracorporeal membrane oxygenation (ECMO).

Table 49.2: Complications of mechanical ventilation

From endotracheal intubation

Atelectasis, perforation of trachea/esophagus, avulsion of vocal cords, subglottic stenosis, superimposed infection.

From barotrauma

Interstitial emphysema, pneumothorax, mediastinum, pericardium, peritoneum; subcutaneous emphysema.

Multiple Choice Questions

- Spot the wrong observation:
 - An "infant immobilization board" is a useful device for pre-procedure restraint and positioning
 - Femoral puncture is best avoided
 - Subdural puncture is as safe as lumbar puncture
 - Fine needle aspiration cytology (FNAC) is useful for cytological and bacteriological examination of a lymph node or a mass
- All of the following are contraindications for intraosseous infusion, except:
 - Osteogenesis imperfecta
 - Cellulitis
 - Infected burns
 - A benign tumor anywhere in the skeleton
- Helmich's maneuver is relevant to:
 - Foreign body in the airway
 - Foreign body in the gastrointestinal tract
 - Foreign body in the ear
 - Foreign body in the nose
- Pick up the wrong observation:
 - Indicated when subdural effusion or hematoma is suspected
 - In children, bone marrow should best be done from the sternal site
 - Saline can also be administered slowly by rectal infusion
 - Arterial puncture is indicated for blood gas analysis and invasive blood pressure monitoring
- True statements about exchange transfusion include each of the following, except:
 - Any nonobstructive jaundice with a serum bilirubin of 20 mg/dL or more in full term and 15 mg/dL in preterms is an indication
 - Donor blood/plasma should be fresh (<3 days old)
 - Room temperature should be around 27°C
 - No late (delayed) complications are known

Answers

1. C 2. D 3. A 4. B 5. D

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

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BOOKS/MONOGRAPHS

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BACKGROUND

Laboratory testing is only the first of many challenges in pediatric medicine. Children often acquire diseases that differ from those of adults, and compared with adult disorders, many pediatric diseases are low in frequency. Children are not little adults. Their unique development, nutrition, growth, and diseases create challenges for pediatric laboratory medicine. As a general rule, laboratory tests reflect the physiologic changes associated with diseases and their treatment. For pediatric patients, this assessment occurs within the context of growth and development.

BLOOD EXAMINATION

The complete blood count (CBC) is a commonly ordered laboratory test. Tests included in a CBC include:

- Hemoglobin (Hb or Hgb)
- Hematocrit (Hct)
- Red blood cell count (RBC)
- Erythrocyte indices, such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)
- White blood count (WBC)
- A differential WBC count
- Platelets.

Total Leukocyte Count (TLC)

Blood is drawn into the WBC pipette upto the 0.5 mark. To make a dilution of 1:20, WBC fluid is drawn up to the 11 mark. These are mixed well. Then, after discarding first 2 or 3 drops, WBC counting chamber is charged with this fluid in the same way as in case of the RBC count. Leukocytes are counted in four large corner squares. Box 50.1 presents the causes of leukocytosis and leukopenia.

Total leukocyte count = $50 \times \text{No. of cells counted/mm}^3$

Collection

For investigations needing small amount of blood, such as hemoglobin estimation, peripheral smear and counts,

Box 50.1 Causes of leukocytosis and leukopenia**Leukocytosis**

Trauma, inflammation, acute infection, dehydration, hemoconcentration, cancer such as leukemia, medications such as corticosteroids.

Leukopenia

Bone marrow disorders, viral infections, severe bacterial infections, cancer medications include chemotherapy, antibiotics, anticonvulsants.

finger or heel prick method of obtaining blood suffices, unless the investigations are to be actually done at a later stage and it is desirable to have the blood collected. In the latter situation and when larger amount of blood is required, a venipuncture, preferably from an antecubital vein, is indicated. Femoral puncture should, as far as possible, be avoided in view of its potential hazards. For hemoglobin estimation, cell count, etc. 1 mL blood is collected in a 5 mL glass vial with 0.04 mL of the 10% ethylenediaminetetracetic acid (EDTA) disodium salt solution. The tests must be carried out within 12 hours of collection of blood.

Blood grouping and cross-matching requires 5 mL of blood in a 5 mL glass vial without any anticoagulant. The tests need to be done within 12 hours. Biochemical investigations such as serum bilirubin, urea, proteins, cholesterol, liver function test (LFT) and electrolytes require 5 mL of blood in a 5 mL glass vial without any anticoagulant. Maximum preservation time is just 48 hours.

In case of prothrombin time, 4.5 mL blood is required to be collected in a glass tube containing 0.5 mL trisodium citrate. Maximum preservation time is sheer 2 hours. For glucose, 5 mL blood is collected in a glass vial with 5 mg sodium fluoride. Maximum preservation time once again is 2 hours. For enzymes (transaminases, phosphatase), 5 mL blood in a glass vial without any anticoagulant suffices. Maximum preservation time here too is just 2 hours. Iron and its binding capacity need 5 mL of blood in acid-washed tubes. The tests must be carried out as early as feasible. For blood culture, 5 mL of blood is required for each of the two tubes, one with meat broth and the other nutrient broth with bile salts.

Hemoglobin

The most accurate method of estimating hemoglobin is photoelectric method. The most popular method is, however, acid-hematin method which employs the Sahli hemoglobinometer. This method employs acid hematin in a glass tube as a standard of comparison. The hemoglobin in the diluting tube is converted to acid hematin by addition of N/10 HCl. The method consists of placing N/10 HCl in the hemoglobinometer diluting tube up to the mark 10% (the lowermost mark).

Blood is drawn in a hemoglobin pipette upto 20 cm mark and transferred in to the diluting tube. The mixture is rinsed well. After 10 to 20 minutes, distilled water is added drop by drop. Mixing is attained either by inverting the tube or with a glass rod. Addition of water is continued until

the color of the diluting tube matches that of the standard provided with the hemoglobinometer. The hemoglobin level (g/dL) is denoted by the reading against the lower level of the meniscus of the fluid in the diluting tube.

Hematocrit

Using a capillary pipette, the Wintrobe tube (the same employed for erythrocyte sedimentation rate {ESR}) is filled up to the 100 mm mark with blood already treated with an anticoagulant and centrifuged for 30 minutes at 2,500 revolutions per minute (rpm) in a 15 cm radius centrifuge. The hematocrit or packed cell volume (PCV) is denoted by the upper level of the red cell column in percentage.

Red Cell Count

Blood is drawn up to the 0.5 mark in the RBC pipette. This is followed by drawing in up to 101 mark the RBC diluting fluid. Taking care that the fluid does not spill out, the material is mixed well by rotating the pipette in a horizontal position.

Having discarded the first few drops of the mixture, charge the Neubauer counting chamber with it, ensuring that it does not overflow into the bigger grooves.

Count RBC in 80 smallest squares in the four corners and one central big square.

$$\begin{aligned}\text{RBC count} &= \frac{200}{0.02} \times \text{No. of cells counted} \\ &= 10,000/\text{mm}^3\end{aligned}$$

Having dealt with hemoglobin, red cell count and PCV, let us summarize the erythrocyte indices:

- **Mean corpuscular volume (MCV)**

$$= \frac{\text{PVC liter}}{\text{RBC millions}/\text{mm}^3} \text{ in cubic microns}$$

- **Normal value:** 78–94 cubic microns
- **High:** Macrocytic anemia
- **Low:** Microcytic anemia

- **Mean corpuscular hemoglobin (MCH)**

$$= \frac{\text{Hemoglobin g/dL}}{\text{RBC millions}/\text{mm}^3} \mu\text{g}$$

- **Normal value:** 27–32 μg
- **High:** Macrocytic anemia
- **Low:** Microcytic anemia

- **Mean corpuscular hemoglobin concentration (MCHC)**

$$= \frac{\text{Hemoglobin g/dL}}{\text{PVC}} \times 100\%$$

- **Normal:** 32–38%
- **Low (below 32%):** Iron deficiency
- **It cannot exceed:** 38%.

- **Color index**

$$= \frac{\text{Hemoglobin expressed as percentage of normal (14.5g as 100\%)}}{\text{RBC expressed as percentage of normal (5 million as 100\%)}}$$

- **Normal value:** 0.9–1.1
- **About unity:** Recent hemorrhage
- **Low:** Iron deficiency
- **Raised:** Megaloblastic anemia.

Peripheral Blood Film

A clean dry slide is touched to a newly formed drop of blood from finger prick. One edge of a spreader slide is placed over

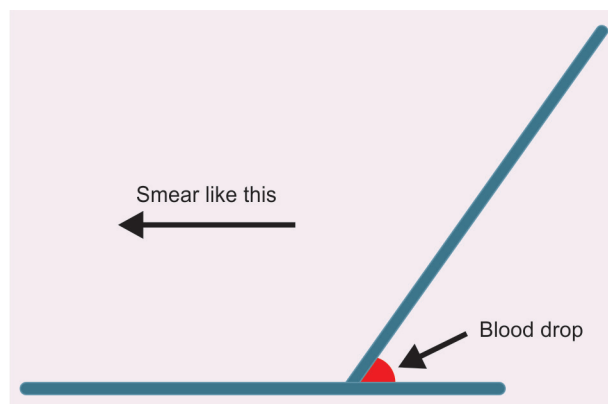


Fig. 50.1: Technique of preparing a peripheral blood film.

the drop of blood smearing across the first slide should be done as shown in (Fig. 50.1). The smear is allowed to dry. For malarial parasite, both thick and thin smears should be prepared. Staining is done by Giemsa stain; thin smear needs earlier fixation with methanol for a couple of minute. For information concerning white and red cells, staining is done either with Leishman stain or Wright stain.

Differential Leukocyte Count (DLC)

A well-stained peripheral blood film is examined under the oil immersion lens. At least 100 white cells with individual identification are counted proceeding from one side to the other. The individual cell types are expressed as a percentage.

Erythrocyte Sedimentation Rate

Erythrocyte sedimentation rate is a measurement of the distance (mm) covered by the upper level of the red cell column in first hour. **Westergren method** consists of drawing into Westergren pipette 0.5 mL of 3.8% sodium citrate solution up to the 200 mark. The pipette is then fixed in a stand and sealed to a cork at the bottom. ESR is read directly from the tube after 1 hour. **Wintrobe method** consists of filling the Wintrobe tube up to the 100 mark with double oxalated blood. It is allowed to stand vertically in a stand for 1 hour. ESR is denoted by the reading on the tube.

Reticulocyte Count

In a glass test tube poured a drop of cresyl blue solution followed by two drops of blood to be tested. These are mixed. After allowing to stand for 15 minutes, the tube is shaken gently.

Out of this stuff, one drop is taken on a glass slide and a smear is prepared. On microscopic examination under oil immersion lens, you would see reticulocytes as red cells with fine deep yellow granules in a network against pale blue RBC. At least 100 red cells need to be counted to ascertain the number of reticulocytes which should be expressed as percentage of red cells.

Platelet Count

Rapid method consists in putting a drop of 14% magnesium sulfate solution over the finger puncture that has been

872 earlier wiped dry and then touching a glass slide to the finger. The blood on slide is allowed to be smeared and then dried. It is stained with Wright stain.* Platelets are counted per 1000 red cells and platelet count is calculated from red cells.

Direct method consists in drawing freshly prepared platelet solution** to the 0.5 mark in red cell pipette. Tip of the pipette is wiped and blood to 0.5 mark is drawn so that the platelet solution reaches the 1.0 mark. The tip is again wiped, and the pipette is filled with platelet solution to the 101 mark. After mixing, count is conducted in hemocytometer as for red cell count.

URINE EXAMINATION

Collection

Make sure that collection of urine is made in a container that is chemically clear. Else, the results can be misleading. Medicine bottles which are not adequately washed may carry traces of syrup and be responsible for erroneous results. Extra care needs to be exercised in collecting urine in females, especially at puberty when contamination with vaginal discharge or menstrual blood may affect the results. Contamination with feces also needs to be avoided. For collection of urine for culture, a clean catch midstream specimen in a sterile container with no preservative at all is a must.

Occasionally, a suprapubic puncture may be needed in sick neonates and small infants. Such a puncture is done under aseptic conditions 1–2 hours after feeding. The infant is placed in a supine position with hips and knees flexed to 90° and the thighs abducted. A 21 gauge needle attached to a 10 mL syringe is introduced vertically 1–2 cm above the symphysis pubis in the midline. Once the urinary bladder is pierced at a depth of 1.5–2 cm, you may aspirate urine in the syringe, and collect in the appropriate container. Suprapubic puncture is safe. Occasionally, slight hematuria may occur.

Physical Examination

- **Color:** Normal urine is yellow amber in appearance due to presence of urochrome. A fresh sample is clear, but may become cloudy or turbid on standing. Presence of phosphates may render even a freshly voided sample cloudy. The change in color may point to the cause as clarified below:
 - **Orange:** Restricted fluid intake leading to concentrated urine; fever; urobilin; drugs such as pyridium
 - **Dark-brown:** Altered blood as in methemaglobinuria; porphyrin;
 - **Red blood:** Beetroot, aniline dyes, drugs, such as pyridium
 - **Purple red:** Phenol; phenolphthalein
 - **Port wine:** Porphyrin
 - **Brownish black:** Alkaptonuria

- **Greenish:** Biliverdin, carbolic acid
- **Blue:** Methylene blue, indigo blue.

Reaction in order to find the pH of urine, one end of a indicator paper is dipped in a fresh sample of urine. The pH is indicated by noting the reading on standard scale against the resultant color. Specific gravity A minimum of 40 mL of urine is put into a 50 mL measuring cylinder. The specific gravity is read from the urinometer which is gradually lowered into the container and allowed to be steady, ensuring that it is not in contact with the bottom or sides of the container.

Chemical Examination

Albumin for the conventional boiling test, test tube is filled 3/4th with the urine sample (filtered/centrifuged, if cloudy). If, on boiling the upper part of the tube content, a turbidity appears, protein or phosphates are present. In case of protein, the turbidity persists despite addition of a few drops of 10% acetic acid. The presence of albumin can be further confirmed by warming equal amounts of urine and Exton's sulfosalicylic acid, resulting in white cloudiness.

Grading of amount of proteinuria may be done as under:

● Slight cloudiness:	Traces	(0.005–0.01 g%)
● Definite cloudiness:	1+	(0.01–0.05g%)
● Cloudiness along with flocculation	2+	(0.05–0.2g%)
● Cloudiness along with remarkable flocculation:	3+	(0.2–0.5g%)
● Cloudiness along with precipitation:	4+	(0.5 g% or more)

Another method of detecting proteinuria in the so-called, **dipstick test** (Uristix, Albustix), a very sensitive tool that detects primarily albumin. It is reported as:

- Negative traces
 - 1+ closest to 30 mg/dL
 - 2+ closest to 100 mg/dL
 - 3+ closest to 300 mg/dL
 - 4+ greater than 2 g/dL

False negative results may be because of highly concentrated urine sample, gross hematuria or contamination with chlorhexidine or benzalkonium. For measuring 24-hour urinary protein, having measured the total volume of the 24-hour collection, filtered it and brought the specific gravity below 1010 (if it is more) and added 10% acetic acid (if it is alkaline), fill the Esbach albuminometer tube with the sample up to the mark "U". To this, add Esbach reagent up to the "R". Having closed the tube with a rubber stopper, let the urine and reagent mix by inverting it a few times. After allowing the albumometer stay as such for 24 hours, note the level of the precipitate on the scale. This gives the 24-hour protein loss per liter

* Wright stain for blood is prepared by grinding 100 mg of powdered stain in mortar. To the material is added 60 mL of alcohol. Evaporation of alcohol may cause precipitate formation on slide. In that case, 2 mL of methyl alcohol/10 mL of staining solution should be added.

** Platelet solution is prepared by mixing 3.8 g sodium citrate, 0.2 mL neutral 40% solution of formaldehyde and 0.05 g brilliant green cresyl blue in 100 mL of water.

of urine in grams. False negative results may be because of radiographic contrast medium or drug therapy with cephalosporin, penicillin, sulfonamide or tolbutamide.

Sugar to 5 mL of Benedict qualitative reagent in a test tube, add 0.5 mL (8 drops) of urine and shake well. Then, boil over naked spirit lamp flame for 2 minutes and allow to cool for 5 to 10 minutes. Blue coloration means no sugar.

Clear green to brick red indicates varying amount of sugar as shown below:

• Clear green	Negligible
• Green with precipitate	Traces
• Yellow with precipitate	0.5%
• Orange with precipitate	1.0%
• Brick red with precipitate	2.0%

Remember, drugs such as aspirin, morphia, chloral hydrate, paraldehyde and PAS may reduce the Benedict agent even when there is no glycosuria.

Ketones identification of ketones in urine is done by the Rothera test. About 10 mL of freshly voided urine in a test tube is saturated with Rothera's mixture consisting of 99 parts of ammonium sulfate and 1 part of sodium nitroprusside. Pour 2 mL of strong ammonia gently along the side of the tube. Let it stand for 5 minutes. A purple color at the junction of urine and ammonia solution indicates positive reaction of ketone bodies.

Bile salts to a 8–15 cm column of fresh urine in a beaker, add finely powdered dry sulfur. If bile salts are present, the sulfur particles would sink. Else, these would float on the surface.

Bile pigments for Fouchet test is the most sensitive for this purpose. It consists in adding 2.5–5 mL of barium chloride solution to 5–10 mL of fresh urine (if it is alkaline or neutral, acidify it with few drops of acetic acid). All this is mixed well and then filtered. To precipitate (residue) on the filter paper, add a drop or two of Fouchet reagent. A green color or a blue color indicates bilirubin—the former, the biliverdin, and the latter, the cholesteryramine.

Occult blood, addition of 1 mL benzidine reagent (made by dissolving 4 gm benzidine in 100 mL glacial acetic acid) and 1 mL hydrogen peroxide in 1 mL urine sample leads to blue coloration in case hemoglobin is present.

Porphyryns, addition of 0.5 mL Ehrlich reagent to 5 mL urine in a test tube may cause a distinct red color, indicating that either urobilinogen or porphobilinogen is present. To this, add 2 mL chloroform, mix and let the chloroform from the lower layer. If the chloroform layer remains colorless, urine contains only porphobilinogen. If, on the other hand, it becomes pink, urobilinogen is present in the urine sample.

Phenylpyruvic acid, a drop of 10% ferric chloride is poured on a filter paper which had been made wet with urine and then allowed to dry. The resultant green color denotes increased urinary level of phenylpyruvic acid and thereby phenylketonuria (PKU).

Ferric chloride test may be negative in some cases of PKU. Also, it may be positive in other types of aminoaciduria and when drugs such as aspirin, phenothiazines, etc. have been administered.

Urine Microscopy

For microscopic examination, 10–12 mL urine is centrifuged for 5 minutes at 800–1,000 rpm. The supernatant is poured off, leaving behind 0.5 mL stuff in which sediment is resuspended by brisk agitation. Drops of sediment are placed on a slide and examined under the microscope with or without coverslip for RBC, WBC, epithelial cells, casts (red cell, white cell, mixed, granular, semigranular, hyaline), crystals (calcium oxalate, uric acid, cystine, urate, triple phosphate, sulfonamide), bacteria, protozoa and yeasts. The results are expressed in terms of number per high power field.

Generally speaking, more than five red or white cells per high power field are considered abnormal. Whereas hyaline and granular casts may occasionally be a normal finding, the detection of tubular casts, especially in the presence of an abnormal number of red or white cells, certainly points to the existence of a renal disorder.

STOOL EXAMINATION

Collection

For routine examination (gross naked eye and microscopic for ova, cysts and trophozoites), stools need to be collected in a clean, dry and covered container, ensuring that there is no contamination with urine and the container is not sterilized by chemical disinfectants. If delay is anticipated in transporting the sample to the laboratory, it is a good idea to collect the sample in 3% neutral glycerol in 0.6% sodium chloride solution using phenolred as an indicator. The sample deserves to be discarded if the indicator color turns yellow.

Enterobius vermicularis is best detected by examination of the scrapings of the anal and perianal region.

For stool culture, you must collect a rather large sample of mucus-containing stuff, preferably in a medium which not only stabilizes the pH, but also prevents the death and dehydration of the bacteria before culture. Buffered glycerol saline broth is most suitable for this purpose. The composition of this broth is NaCl 4.2 g, K_2NHO_4 3.1 g, KH_2PO_4 1.2 g, glycerol 300 mL, water 700 mL, and phenolred as the coloring agent.

Microscopy

Direct

Place a drop of sodium chloride solution at one end of a clean slide and a drop of Lugol iodine at the other end. To each, add a small portion of the stool sample. Each separation is covered with a cover slip carefully, ensuring there is no entry of the air bubbles. Microscopic examination needs to be done under high as well as low power, shutting down the light to a great extent. Concentration since direct microscopy may miss ova and cysts when infection is not severe, it is often necessary to employ one of the concentration techniques.

Formalin-ether sedimentation technique consists in emulsifying a portion of stools measuring 2–3 cm in diameter in 30–50 mL of saline. About 10 mL of emulsion is strained through two layers of wet gauze into a 15 mL centrifuge tube with a conical tip. This is centrifuged at a

874 moderate speed for a few minutes and the supernatant decanted. The sediment is resuspended in fresh saline, centrifuged and decanted as before. The process may be repeated if necessary, especially in case supernatant is still cloudy. To the sediment is added 10 mL of 10% formalin. After mixing thoroughly, it is allowed to stand for 5 minutes. Then, 3 mL of ether is added. The tube is sealed and shaken vigorously.

Following centrifuging at low speed, 4 layers result. At the bottom is a small amount of sediment containing most of the parasites. Above that is a layer of formalin. On top of formalin layer is a plug of fecal debris. At top there is a layer of ether. The plug of debris from the sides of tube is freed by ringing with an applicator stick. The top three layers are decanted. The remaining sediment is mixed with the small amount of fluid draining back from the sides of the tube. Finally, iodine or unstained mounts may be prepared in the usual manner for microscopic examination.

Zinc sulfate centrifugal floatation technique consists in emulsifying 1 mL of stool sample in 10 mL of tap water. The emulsified sample is filtered through two layers of gauze. The mixture is centrifuged for 1 minute at 26000 rpm and the supernatant fluid poured off. Then fresh water is added and the stuff mixed well and centrifuged again. This process is repeated 3–4 times, remembering that for the final emulsification 33% zinc sulfate solution is substituted for the saline. The suspension is centrifuged at top speed for 1 minute. This way eggs and cysts rise to surface whereas trophozoites get destroyed.

Disturbing the supernatant as little as possible, several loops full of the surface film are transferred to a glass slide. After adding a drop of iodine, mixing and covering with a coverslip, microscopic examination is carried out. Figure 50.2 depicts microscopic appearance of ova/ eggs/ cysts of select protozoa and helminths in stool samples.

Occult Blood

This may be detected by the benzidine test which consists in emulsifying 1 mL of stool sample in 10 mL of water containing 5 drops of glacial acetic acid and centrifuging for 1 minute to separate large stool particles. To 1 mL benzidine solution in a clean test tube is added 0.5 mL 0.6% hydrogen peroxide. Allow it to stand for at least 5 minutes and preferably for 15 minutes for development of maximal color.

Appearance of blue color denotes a positive reaction which should be categorized as below:

• Faint blue	Traces
• Blue green (slowly)	+
• Green blue	++
• Blue (immediately)	+++
• Dark blue (immediately)	++++

Fat Globules

To a 1–2 mL pellet of stool sample on a glass slide, alcoholic solution of the dye, Sudan III or IV is added and mixed well with an applicator stick. Then is added 1 drop of 0.9%

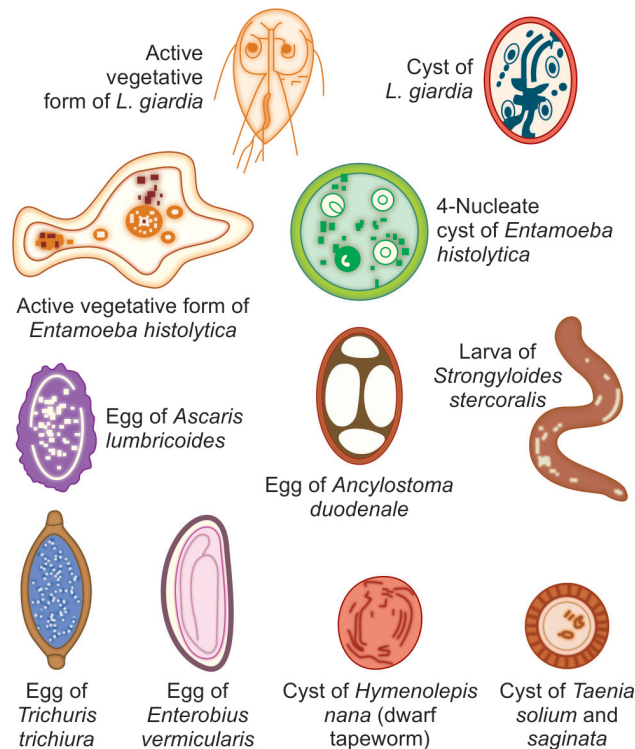


Fig. 50.2: Microscopic appearance of important protozoa and helminths in stool samples.

saline solution. The preparation is covered with a coverslip and examined under the microscope. Flat globules appear pink.

This rough method of testing for steatorrhea may be expressed as under:

• 0–2 globules	0 to +
• 3–5	+
• Intermediate amount	+ to +++
• Half of visible material	++++

Reducing Substances

In order to test for reducing substances (sugar) in suspected carbohydrate intolerance/malabsorption, a small amount of stool sample is taken in a clean test tube and to it four times the volume of water is added. The two are mixed well. The mixture is centrifuged.

The supernatant fluid is transferred to a test tube and to it is added 5 mL of Benedict qualitative reagent. Having shaken well, the mixture is boiled over a naked spirit lamp flame for a couple of minutes. Changes in color varying from green with precipitate to brick-red with precipitate denote presence of sugar between traces to +++.

Stool pH

Acidic pH is a hallmark of lactose intolerance. The test may be conducted by employing a wide range pH paper strip.

CEREBROSPINAL FLUID EXAMINATION

The technique of obtaining cerebrospinal fluid (CSF) from the spine lumbar puncture (LP) is detailed in Chapter 49 (Pediatric Practical Procedures).

Collection

Make sure you collect the CSF in sterile capped vials and transport the vials quickly to the laboratory to safeguard against lysis of cells.

Examination

- **Pressure:** For this, employ the special manometer. The reading is most accurate when the child is relaxed with the neck and legs being extended. Normal range is 60–160 or even 200 mm of water.
- **Appearance:** Compare the color with that of distilled water against a white background. Note if it is clear (normal), turbid, purulent, xanthochromic (always abnormal after the neonatal period), or frankly hemorrhagic (traumatic tap, subarachnoid hemorrhage). Microscopy to 4 drops of CSF, add 4 drops of CSF diluting fluid in a test tube. Wait for 10 to 15 minutes.

Charge the well-cleaned Neubauer counting chamber with stained fluid and cover with the cover slip. Focus the lines of the chamber under the microscope, first under low power and thereafter high power. Count the white cells, both polymorphs and lymphocytes, in the 4 large squares. It is advisable to count the cells thrice and take mean of the three readings so that technical error is minimized. The mean, thus obtained, multiplied by 5 gives the number of white cells/cmm. Express also the percentage of polymorphs and lymphocytes.

For red cell count, the procedure is same except that (1) CSF is not diluted before charging the counting chamber, and (2) Only one chamber may suffice for counting unless

a very large number of red cells are present; in the latter situation counting may be done in 4 or 8 small squares. The number of red cells counted in a large square gives the number of red cells/cmm in the CSF.

- **Protein:** To 2 mL of Pandy reagent in a test tube, add one drop of CSF. The line of CSF drop is followed by cloudiness which varies depending on the amount of globulins present. It may be graded from 0–4.
- **Sugar:** To 5 test tubes containing 1 mL of Benedict qualitative reagent, add 0.05 mL, 0.1 mL, 0.15 mL, 0.2 mL and 0.25 mL of CSF serially. Notice the green reduction after boiling each tube for 5 minutes. Occurrence of such a reduction in tube 1 means 50 mg% sugar, in tube 2 means 40–50 mg% sugar, in tube 3 means 30–40 mg% sugar, in tube 4 means 20–30 mg% sugar and in tube 5 means 10–20 mg% sugar. When none of the tubes shows any green reduction, it means the sugar content is less than 10 mg%. The CSF sugar is normally about half of the blood sugar.
- **Culture:** It is advisable to always send a sample of CSF for culture for bacteria and, if indicated, for acid-fast bacilli (*Mycobacterium tuberculosis*) or fungi.
- **Gram staining:** When meningitis is on the card, CSF is centrifuged and a smear of the fluid made. It is allowed to dry and then subjected to Gram staining. Gram-positive bacteria appear dark whereas Gram-negative ones appear pink.
- **Ziehl-Neelsen staining:** In suspected tuberculous meningitis (TBM), it is important also to microscopically examine a Ziehl-Neelsen stained preparation for acid fast bacilli (AFB).

Multiple Choice Questions

1. Spot the wrong observation:
 - A. Most accurate method for estimating hemoglobin is photoelectric method
 - B. For malarial parasite, both thick and thin blood smear are needed
 - C. ESR is measure of the distance covered by the upper level of the red cell column in mm in first hour
 - D. At least 20 red cells must be counted for reticulocyte count
2. Incorrect observation for blood required for different test is:
 - A. Hemoglobin, cell count, etc.—1 mL
 - B. Serum bilirubin, urea, proteins, cholesterol, liver function tests, electrolytes, etc.—5 mL
 - C. Blood grouping and cross-matching—1 mL
 - D. Blood culture—5 mL
3. True observations about benzidine test for occult blood in stool include each of the following, except:
 - A. One mL of stool sample is sufficient
 - B. Benzidine test involves not only benzidine solution but also hydrogen peroxide
 - C. Appearance of blue color denotes positive reaction
 - D. Faint blue color denotes 3 plus occult blood
4. Which of the following is incorrect about urine color?
 - A. Orange: restricted fluid intake
 - B. Portwine: Porphyrin
 - C. Brownish black: Hematuria
 - D. Red blood: Beetroot, aniline dye, drugs like pyridium

contd...

5. Spot the wrong entry in Dipstick test:

- A. 1+: closest to 30 mg/dL
- B. 2+: closest to 100 mg/dL
- C. 3+: closest to 300 mg/dL
- D. 4+: greater than 1 g/dL

Answers

1. D 2. C 3. D 4. C 5. D

FURTHER READING

JOURNAL ARTICLE/ BOOK CHAPTER

1. King AWE, King A. Evolving laboratory techniques in resource-limited world. *Asian J Lab Invest* 2015;23:134–141.
2. King AWE, King A, Neelsen PE. Pediatric-centric tests. In: King AWE (ed): *Medical Laboratory Techniques*. Toronto: Academicia 2012:213–255.

BOOK/MONOGRAPH

1. Morley JKS. *Pediatric Laboratory Techniques*, 8th edn. Tokyo: United Publishers, 2009.

SECTION 9

Pediatric Syndromes

Section Outline

51. Pediatric Syndromes

- **Aarskog syndrome:** Mild to moderate short stature, rounded face, facial edema, hypertelorism, ptosis, small nose with anteverted nares, broad philtrum, maxillary hypoplasia, hypodontia, brachydactyly with clinodactyly of fifth finger, simian crease, prominent umbilicus, inguinal hernias, shawl scrotum, cryptorchidism.
- **Aagenaes syndrome:** A form of idiopathic familial intrahepatic cholestasis in which cholestasis is accompanied by lymphedema of the lower extremities.
- **Abetalipoproteinemia (acanthocytosis):** Progressive ataxia, retinitis pigmentosa, malabsorption, hypocholesterolemia, abetalipoproteinemia, thorny red cells (acanthocytes); autosomal recessive.
- **Acanthocytosis:** See abetalipoproteinemia.
- **Acrodermatitis enteropathica (Brandt syndrome):** Chronic diarrhea (frequently steatorrheic), dermatosis usually around body openings, alopecia, paronychia; frequently conjunctivitis and blepharitis; zinc deficiency; familial; autosomal recessive.
- **Adenosine-deaminase deficiency:** Severe combined immunodeficiency (SCID), low enzyme levels in red cells; autosomal recessive.
- **Alagille syndrome (arteriohepatic dysplasia):** Unusual facial features like broad forehead, deeply set, widely spaced eyes, long, straight nose, underdeveloped mandible; ocular abnormalities (posterior embryotoxin), cardiovascular abnormalities (pulmonary stenosis, tetralogy of Fallot), vertebral arch defects (peripheral butterfly vertebra), tubulointerstitial nephropathy, growth retardation, defective spermatogenesis; complications include neurologic evidence of vitamin E deficiency, pruritus, xanthomata.
- **Albright syndrome (fibrous dysplasia of bone):** Skin pigmentation, short stature, precocious puberty, areas of osseous rarefaction resembling cysts, advanced bone age, fractures.
- **Alice-in-wonderland syndrome:** Perceptual distortion of shape, size, color and reciprocal position of objects; seen in Epstein-Barr virus (EBV) infection, epilepsy, hallucinogenic drugs, schizophrenia, and migraine, etc.
- **Alpha-1-antitrypsin deficiency:** Persistent jaundice (obstructive) in a newborn, cirrhosis, adult emphysema; autosomal recessive.
- **Ataxia telangiectasia:** Progressive ataxia, choreo-athetosis, telangiectasia of conjunctiva, face, elbows and knees; autosomal recessive.
- **Beckwith syndrome (Beckwith-Wiedemann syndrome):** Macroglossia, macrosomia, omphalocele, hyperplasia of kidneys and pancreas, proneness to Wilms' tumor; hypoglycemia, prominent facial nevus flammeus.
- **Berger disease:** Gross hematuria (intermittent), benign focal glomerular lesion.
- **Bloom Syndrome:** Dwarfism, congenital telangiectatic erythema over malar area of face, nose and lips, photosensitivity, small narrow face, high-pitched voice, protruding ears; diminished immunoglobulins; high frequency of chromosomal breakage.
- **Blue diaper syndrome:** Failure to thrive (FTT), blue discoloration of diaper right from early infancy, irritability, constipation, infections, recurrent fever of unknown etiology, high blood urea, hypercalcemia, extensive nephrocalcinosis.
- **Brandt syndrome:** See acrodermatitis enteropathica.
- **Brachmann-de-Lange syndrome:** Prenatal onset growth deficiency in weight and height, retarded osseous maturation, low-pitched weak growling cry, mental retardation, microbrachycephaly, bushy eyebrows with synophrys, depressed nasal bridge with anteverted nares, long philtrum, thin upper lip, high arched palate, micrognathia, hirsutism, phocomelia, micromelia, undescended testes, hypospadias.
- **Caffey disease (infantile cortical hyperostosis):** Nonsuppurative, tender, painful swellings over the flat and tubular bones (subcutaneous tissue and joints are spared), irritability, fever, anemia, leucocytosis, high erythrocytes sedimentation rate (ESR) and alkaline phosphatase; X-ray of bones reveals cortical hyperostosis; self-limited; corticosteroids indicated in advanced cases.
- **Cardio-facio-cutaneous syndrome:** Mild to severe mental retardation, hypotonia, nystagmus, mild hydrocephalus, cortical atrophy, hypoplasia of frontal lobes, postnatal growth retardation, delayed bone age, macrocephaly, large prominent forehead, shallow orbital ridges, antimongoloid slant, epicanthal folds, hypertelorism, ptosis, exophthalmos, prominent philtrum, webbed neck, congenital cardiac defects especially atrial septal defect (ASD) and pulmonic stenosis, sparse curly hair, lack of eyelashes and eyebrows, hyperkeratosis or ichthyosis-like skin lesions.
- **Cat eye syndrome:** Cardiac defects in more than 33% patients, including total anomalous pulmonary venous return, ventricular septal defect (VSD), ASD; mild mental retardation, mild hypertelorism, antimongoloid slant of palpebral fissure, anal atresia with rectovestibular fistula, coloboma of iris.

- 880 ■ Caudal regression syndrome:** Anorectal malformations, urogenital anomalies, varying degrees of lumbosacroccygeal agenesis; most extreme form is represented by mermaid fetus (sirenomelia); supposed to be an embryonal defect dating back to the primitive streak stage during third week of intrauterine life; recently diabetes mellitus has been incriminated as a possible cause.
- **Chédiak-Higashi syndrome:** Semialbinism, photophobia, nystagmus, excessive sweating, generalized lymphadenopathy, hepatosplenomegaly, pale optic fundi, pyogenic infections, progressive neurologic manifestations; grey-green granules in the cytoplasm of neutrophils and extremely large red granules in the eosinophils and myelocytic cells of the marrow; familial, autosomal recessive; fatal.
 - **Chotzen syndrome (cranio-oculodental syndrome):** Characteristic facies with asymmetry, low hairline, ptosis, parrot-beaked nose, partial craniosynostosis (specially involving coronal or sphenobasilar sutures).
 - **Chronic granulomatous disease:** Frequent pyogenic infections; nitroblue tetrazolium test; X-linked recessive.
 - **Cleidocranial dysostosis:** Absent clavicles, delayed closure of fontanelles; autosomal dominant.
 - **Cockayne syndrome:** Dwarfism, ankylosis, kyphosis, pinched facies, thin nose, sunken eyes, prognathism, mental retardation, partial deafness, ataxia, photosensitivity, optic atrophy, attenuation of retinal vessels; hereditary.
 - **Congenital chloridiarrhea:** Neonatal diarrhea, low serum chloride and potassium, metabolic alkalosis; autosomal recessive.
 - **Costello syndrome:** Postnatal growth retardation, delayed bone age, mental deficiency, macrocephaly, coarse facies, low set ears with thick lobes, antimongoloid slant, epicanthal folds, macroglossia, depressed nasal bridge, thin deep-set nails, cutis laxa, curly sparse hair, deep plantar, palmar creases, short neck, tight achilles tendon, hyperextensible fingers, congenital heart defects, especially pulmonary valve stenosis, VSD, ASD, hypertrophic cardiomyopathy.
 - **Crigler-Najjar syndrome:** Type 1, severe neonatal jaundice, autosomal recessive. Type 2, mild neonatal jaundice, autosomal dominant, responds to phenobarbital.
 - **Cause:** Glucuronyl transferase deficiency.
 - **Cri du chat syndrome (deletion 5p syndrome):** Low birth weight (LBW), slow growth, cat-like cry, hypotonia, mental retardation, microcephaly, hypertelorism, epicanthal folds, variable types of congenital heart disease, simian crease, cleft lip/palate, bifid uvula.
 - **Cystinosis:** Failure to thrive (FTT), cystine crystal deposits in eyes, marrow and reticuloendothelial system; autosomal recessive.
 - **Deletion 3p syndrome:** Prenatal onset of growth deficiency, hypotonia, severe to profound mental retardation, microcephaly with flat occiput, ptosis, epicanthal folds, prominent nasal bridge, anteverted nares, long philtrum, micrognathia, postaxial polydactyly.
 - **Dermatitis herpetiformis:** Skin eruptions (vesicular and itching), malabsorption consistent with celiac disease. Skin lesions show slow response to elimination of gluten from diet.
 - **Dermochondrocorneal dystrophy of francois:** Xanthoma-like skin nodules, abnormal ossification of cartilage of hands and feet, reduced visual acuity due to white, irregular corneal opacities.
 - **Diamond-Blackfan anemia:** Congenital pure red cell hypoplastic anemia.
 - **Diastematomyelia:** Progressive paralysis, anesthesia, neurogenic bowel and bladder due to the traction caused by the bony spur through the lower spinal cord.
 - **DiGeorge syndrome:** Defects of heart and face, repeated infections, neonatal tetany; absent thymus and parathyroids; normal immunoglobulins.
 - **Donohue syndrome (leprechaunism):** Hairy old-man's appearance, wrinkled skin, hypertelorism, prominent eyes, broad and protruding nose, large and low-set ears; in females nipples, labia minora and clitoris are hyperplastic.
 - **Down's syndrome (trisomy 21):** Hypotonia, flat facies, slanted palpebral fissures, small ears, brachycephaly, mild microcephaly, endocardial cushion defects, sandal toes, simian crease, relatively small penis, decreased testicular volume, primary gonadal deficiency.
 - **Dubin-Johnson syndrome:** Intermittent obstructive jaundice, black pigment in liver biopsy; autosomal recessive.
 - **Dubowitz syndrome:** Prenatal onset growth retardation, delayed osseous maturation, mental retardation, muscular hypotonia, hoarse cry, microcephaly, broad nasal tip, short palpebral fissures, eczema-like skin disorder on face and flexural areas, brachyclinodactyly of fifth finger, delayed dentition, missing teeth.
 - **Edwards syndrome (trisomy 18):** Prominent occiput, low-set malformed auricles, short palpebral fissures, small oral opening, clenched hands, overlapped index finger over third finger and fifth finger over fourth, absent distal crease on fifth finger, hypoplasia of nails, short sternum, small nipples, inguinal/umbilical hernia, cryptorchidism, mild hirsutism, VSD, ASD, patent ductus arteriosus, microcephaly, rocker-bottom feet, hypoplastic/absent thumb.
 - **Ebstein anomaly:** Tricuspid valve set in right ventricle, large square cardiac shadow, abnormal electrocardiogram (ECG) and rhythms.
 - **Ehlers-Danlos syndrome:** Hyperelastic and easily scarred skin, easy bruising; hypermobility and recurrent dislocation of joints; of 10 types, autosomal dominant is most common.
 - **Evans syndrome:** Hemolytic anemia, thrombocytopenia.

- **Fabry syndrome:** Cutaneous papules and macules, hyperkeratotic skin, particularly in areas of genitalia and thighs.
- **Familial dysautonomia (Riley-Day syndrome):** Absence of tears, poor perception of painful stimuli, excessive drooling, sweating, skin blotching, paroxysmal hypertension; autosomal recessive.
- **Fanconi anemia:** Congenital malformation of bones of forearm, dwarfism, mental retardation, aplastic anemia developing in toddler; autosomal recessive.
- **Fetal alcohol syndrome:** Prenatal onset and persistence of growth deficiency for length, weight and head circumference, facial abnormalities (short palpebral fissure, epicanthal fold, maxillary hypoplasia, micrognathia, thin upper lip), cardiac defects (septal), minor limb and joint abnormalities, growth and mental deficiency.
 - **Cause:** High level of alcohol ingestion during pregnancy.
- **Fetal caffeine syndrome:** LBW, developmental delay, multiple congenital malformations.
 - **Cause:** Daily/consumption of over 8–10 cups of caffeine drink during pregnancy, providing over 1,000 mg caffeine/day.
- **Floating-harbor syndrome:** Marked postnatal growth retardation, delayed bone age, mild mental retardation, significant speech delay, broad bulbous nose with prominent nasal bridge, short philtrum, wide mouth with thin lips, low posterior hairline, clinodactyly, brachydactyly.
- **Fragile X syndrome:** Long face, prominent forehead, large ears, prominent jaw, macro-orchidism; behavioral problems, even mental retardation;
 - **Cause:** A rare folate-sensitive fragile site in band Xq 27.3; dominant X-linked disorder; gene stands isolated.
- **Freeman-Sheldon syndrome (whistling face syndrome, craniocarpotarsal dysplasia):** Stiff, mask-like facies with flattened facial bones, ptosis, blepharophimosis, narrow, small nose, high-arched palate, microstomia with small tongue and thin protruding lips.
- **Friedreich ataxia:** Cerebellar ataxia due to spinocerebellar degeneration, pes cavus, myocarditis, followed by scoliosis later, at times, diabetes insipidus; autosomal recessive.
- **Fröhlich syndrome:** Obesity, hypogenitalism, growth retardation, diabetes insipidus.
 - **Cause:** Usually intra-cranial tumor.
- **Gilbert syndrome:** Fluctuating unconjugated hyperbilirubinemia (mild) which is aggravated by administration of nicotinic acid; autosomal dominant.
- **Goldenhar syndrome (oculoauriculovertebral dysplasia):** Epibulbar dermoids, preauricular skin appendages, malformations of mandible, sometimes hemivertebrae or fused vertebrae.
- **Goltz-Gorlin syndrome (focal dermal hypoplasia):** Atrophy and linear pigmentation of skin with occasional papillomas, alopecia, dystrophy, malformation of teeth, squint, colobomas of iris, choroid and retina, asymmetry of nasal cartilage, digital anomalies.
- **Gulf syndrome:** Hypervitaminosis A and D resulting from excessive intake of vitamins A and D in fish oil pearls marketed by Gulf countries.
- **Gray baby syndrome:** Following 2–4 days' administration of chloramphenicol, occurrence of manifestations in the newborn such as vomiting or regurgitation, refusal to suck and abdominal distension. In another day or so, the baby develops ashen gray color and becomes limp and severely dyspneic. He may die within one to two days of onset of manifestations.
- **Hallermann-Streiff syndrome (oculomandibulofacial dyscephaly):** Aged, wrinkled appearance, microphthalmia, bilateral cataract, hypomandibulosis, hypotrichosis, parrot-like facies, microcephaly, dental defects, and motor and mental retardation.
- **Hallervorden-Spatz disease:** Progressive rigidity and dementia beginning in late childhood
 - **Cause:** Deposits of iron-containing pigment in globus pallidus and substantia nigra.
- **Hand-Schüller-Christian disease:** Histiocytic infiltration causing triad of bone lesions, exophthalmos and diabetes insipidus.
- **Hartnup disease:** Intermittent ataxia, photodermatitis, psychosis, generalized neutral aminoaciduria; autosomal recessive.
- **Hyper-IgE syndrome (job syndrome):** Recurrent *Staphylococcal* infections, abscesses, skin pigmentation, chronic eczema, red hair; occurs exclusively in boys; IgE levels remarkably high; a cell-mediated immunity defect.
- **Jervell and Lange-Nielsen syndrome (cardioauditory syndrome):** Congenital perceptive deafness (symmetrical), cardiac conduction defects, syncopal attacks, sudden death; autosomal recessive.
- **Job syndrome:** See hyper IgE syndrome.
- **Johanson-Blizzard syndrome:** Prenatal onset growth retardation, mental retardation, sensorineural deafness, microcephaly, hypoplastic or aplastic alae nasi, sparse hair with frontal upsweep, hypoplastic deciduous teeth, absent permanent teeth, imperforate or anteriorly placed anus, caliectasis to hydronephrosis, hypothyroidism of unknown etiology, pancreatic insufficiency with malabsorption.
- **Kabuki syndrome:** Postnatal growth retardation with onset during first year, long palpebral fissure with eversion of lateral portion of lower eyelid, arching of eyebrows with sparse lateral third, short nasal septum, large protuberant ears, preauricular pit, cleft palate, congenital cardiac defects, joint hyperextensibility, persistent fetal finger pad, hearing loss.
- **Kallmann syndrome:** Anosmia, gonadotrophin lack; X-linked recessive.
- **Kartagener syndrome:** Dextrocardia (usually situs inversus totalis), chronic sinusitis, chronic bronchitis/bronchiectasis.

- 882 ■ Kasabach-Merritt syndrome:** Giant hemangioma, platelet trapping and consumption.
- **Kawasaki disease (mucocutaneous lymph node syndrome):** Prolonged high pyrexia, skin and mucous membrane lesions, cervical adenopathy; arthralgia/arthritis, pyuria, proteinuria, mild hepatitis, aseptic meningitis in some; cardiovascular involvement infrequent.
- **Klinefelter (XXY) syndrome:** Relatively tall and slim stature, low upper to lower segment ratio, relatively small testis and penis, inadequate testosterone production, fifth finger clinodactyly, taurodontism, tendency towards behavior problems.
- **Larsen syndrome:** Multiple congenital dislocations, including anterior dislocation of the tibia or the femur, flat facies, frontal bossing, hypertelorism, depressed nasal bridge, talipes equinovarus.
- **Laurence-Moon-Biedl syndrome:** Obesity, hypogonitalism, short stature, retinitis pigmentosa, polydactyly, mental retardation: autosomal recessive.
- **Lazyleukocyte syndrome:** Gingival stomatitis, recurrent upper respiratory infection, otitis, skin infection, intractable persistent pyrexia, leukopenia; a neutrophil defect leading to absence of polymorphonuclear motility from bone marrow.
- **Leigh syndrome:** Subacute necrotizing encephalopathy with progressive neurologic deterioration; early manifestations: feeding difficulties, feeble or absent cry, floppiness; late manifestations: optic atrophy, seizures; autosomal recessive.
- **Leiner disease:** Severe seborrheic eczema, chronic diarrhea, FTT, bacterial infections, abnormal C5 complement function.
- **Léri-Weill syndrome (Dyschondrosteosis):** Short forearms with Medelung deformity and often short lower legs.
- **Lesch-Nyhan syndrome:** Psychomotor deterioration progressing to choreoathetosis and self-mutilation by 2–3 years, abdominal pain, uric acid crystaluria, renal failure, elevated plasma uric acid, absence of an enzyme; X-linked recessive.
- **Letterer-Siwe disease:** Histiocytic infiltration leading to hepatosplenomegaly, purpuric seborrheic eczema.
- **Lowe syndrome:** Cataract, buphthalmos, mental retardation, aminoaciduria; X-linked recessive.
- **Lucey-Driscoll syndrome:** Familial transient unconjugated hyperbilirubinemia:
 - **Cause:** Glucuronyle transferase inhibitor in serum of baby and mother.
- **Maroteaux-Lamy syndrome (pyknodysostosis):** Dwarfism, delayed closure of fontanelles, dysplasia of skull, cortical densities of the bones, short digits with wrinkled skin and nail, parrot-like nose, partial adontia.
- **McCune-Albright syndrome:** Precocious puberty, fibrous dysplasia of bones, feathery edged pigmentation.
- **Meckels syndrome:** Postaxial polydactyly, encephalocele, cystic dysplastic kidneys and hepatic fibrosis; autosomal recessive disorder.
- **Menkes kinky hair disease/syndrome:** Woolly, curly hair, psychomotor deterioration, seizures, low plasma copper and ceruloplasmin; X-linked recessive.
- **Mikity-Wilson syndrome (bubbly lung syndrome):** Respiratory distress, expiratory grunting, chest retraction; cyanosis; occurs in premature infants shortly after birth; X-ray chest shows combined segmental collapse and overinflation.
- **Mulibrey nanism syndrome (perheentupa syndrome):** Prenatal onset of growth retardation, hands and feet appear large as compared to body, dolichocephaly, J-shaped sella turcica, frontal bossing, triangular facies, decreased retinal pigmentation, hepatomegaly, variable fibrous dysplasia, muscle hypotonia, cutaneous naevi.
- **Munchausen syndrome by proxy:** Induced or fabricated symptoms in respect of the child by parents, usually by mother connected with medical profession.
- **MURC association:** An association of Mullerian duct aplasia/hypoplasia (MU) manifesting as genital anomalies, renal agenesis/ectopy (R), and fusion of cervicothoracic vertebrae (C); probable teratogenic origin.
- **Myotonic dystrophy:** Infantile hypotonia, feeding difficulties, mental retardation, cataracts, myocarditis, frontal baldness (later); autosomal dominant.
- **Noonan syndrome:** Epicanthal folds, ptosis, hypertelorism, low nasal bridge, antimongoloid slant, keratoconus, myopia, low-set or abnormal ears, retrognathia, low posterior hairline, short or webbed neck, shield chest, pectus excavatum/carinatum, cubitus valgus, pulmonary valve stenosis, hypertrophic cardiomyopathy, ASD, tetralogy of fallot (TOF), coarctation of aorta, small penis, cryptorchidism, variety of defects in coagulation.
- **Omenn syndrome:** Profound susceptibility to infection, T cell infiltration of skin, gut, liver, and spleen leading to exfoliative erythroderma, lymphadenopathy, hepatosplenomegaly, and intractable diarrhea. Remarkable eosinophilia and persistent leucocytosis in association with combined immunodeficiency. It is fatal, autosomal recessive.
- **Opitz G/BBB syndrome:** Hypotonia, mild to moderate mental deficiency, prominent forehead, ocular hypertelorism, upward or downward slanting palpebral fissure, epicanthal folds, broad flat nasal bridge with anteverted nares, hypospadias, cryptorchidism, bifid scrotum, laryngotracheal cleft, malformation of larynx, trachea-esophageal fistula, hernias.
- **Optopalatodigital syndrome:** Small nose, hypertelorism, broad nasal root, frontal and occipital bossing, cleft palate, growth and mental retardation, irregular fingers and toes, limited elbow extension and wrist supination.
- **Osteopetrosis (marble bone disease):** Thickened fragile bones, pancytopenia, splenomegaly; autosomal recessive.

- **Patau syndrome (trisomy 13):** Holoprosencephaly type defect with varying degrees of incomplete development of forebrain and olfactory and optic nerves, minor motor seizures, severe mental retardation, deafness, moderate microcephaly, microphthalmia, coloboma of iris, cleft lip, cleft palate, low-set ears, abnormal helices, capillary hemangioma, simian crease, VSD, patent ductus arteriosus, ASD, cryptorchidism, hypertonia, hypotonia, hydrocephalus, absent philtrum, cleft tongue, omphalocele.
- **Peutz-Jeghers syndrome:** Melanotic macules on lips and mucous membranes, polyposis of small intestine; autosomal dominant.
- **Penta X syndrome (XXXXX syndrome):** Moderate to severe mental retardation, FTT, microcephaly, short stature, mongoloid slant, short neck, low nasal bridge, low hairline, congenital heart defects, taurodontism.
- **Prader-Willi syndrome:** Obesity, mental retardation, hypogonadism, cryptorchidism.
- **Progeria:** LBW, early growth failure, premature senility, remarkable loss of subcutaneous fat, bald head, absence of eyebrows, atrophic nails, osteoarthritis, arteriosclerosis.
- **Reifenstein syndrome:** Hermaphroditism due to defective virilization from reduced end-organ responsiveness.
- **Rett syndrome:** A previously normal child begins showing at 7–8 months of age early communication dysfunction with autistic features, dementia, loss of purposeful use of hands, typical hand movements, ataxia and seizures; by age 10–12 bedridden because of development of hypertonia and flexed posture; occurs exclusively in females; believed to be a primary abnormality in central monoaminergic system.
- **Rieger syndrome:** Hypodontia, iris anomalies, synechiae extending from the iris to the cornea.
- **Right middle lobe syndrome:** Subacute or chronic pneumonitis, bronchial obstruction, atelectasis; bronchiectasis may result. In addition to pulmonary suppuration, it may be related to asthma or congenital anomalies of bronchi.
- **Riley-day syndrome:** See familial dysautonomia.
- **Ritter disease:** Bright erythematous eruption over face, neck, axilla and groin changing into a wrinkled appearance with ill-defined flaccid bullae filled with clear fluid; areas of epidermis separate when gently stroked (Nikolsky sign); within 2–3 days postinflammatory desquamation; conjunctivitis, pharyngitis, stomatitis; caused by *Staphylococcus aureus*, usually group 1.
- **Robinow syndrome:** Mild to moderate postnatal short stature, macrocephaly, hypertelorism, prominent eyes, downslanting palpebral fissure, small upturned nose, long philtrum, triangular mouth with downward angles, micrognathia, crowded teeth, short forearms, thoracic hemivertebrae, small penis, cryptorchidism.
- **Rothmund syndrome:** Poikiloderma, cataracts, small saddle nose, microdontia, hyperkeratosis of palms and soles, mental retardation.
- **Rotor syndrome:** Neonatal jaundice which persists; 883 autosomal dominant.
- **Rubinstein-Taybi syndrome (Broad thumb-hallux syndrome):** Growth and mental retardation, characteristic facies with beak-like nose, narrow, high palate, prominent forehead, low-set and slightly anomalous ears, palpebral fissures, showing anti mongoloid slant, abnormally wide thumbs and first toes.
- **Russet-Silver syndrome:** Short stature, asymmetry of the body, triangular face, clinodactyly, early sexual development.
- **Schmidt syndrome:** Idiopathic adrenal insufficiency, hypothyroidism, insulin-dependent diabetes mellitus, hypoparathyroidism, gonadal failure; and autoimmune endocrinopathy.
- **Seckel syndrome:** Prenatal onset severe growth retardation, mental retardation, microcephaly with secondary premature synostosis, receding forehead, low-set malformed ears, relatively large eyes with anti mongoloid slant, clinodactyly of fifth finger, simian crease, dislocation of hip, cryptorchidism, only 11 pairs of ribs.
- **Short-rib polydactyly syndromes:** Hydropic appearance, gastrointestinal tract (GIT) and cardiovascular system (CVS) anomalies, dysplastic kidneys, genital hypoplasia, narrow thorax; micromelia, polydactyly; uniformly fatal at or shortly after birth; prenatal diagnosis possible by radiography or ultrasound; autosomal recessive inheritance.
- **Sjögren-Larsson syndrome:** Mental retardation, spastic paralysis, congenital ichthyosis.
- **Smith-Lemli-Opitz syndrome:** Anteverted nostrils, ptosis, syndactyly of second and third toes, hypospadias and cryptorchidism, growth and mental retardation.
- **Sotos syndrome (cerebral gigantism):** Excessive growth (height and weight are significantly large), mild mental retardation, acromegalic facies.
- **Spasmus nutans:** Abnormal posture and movements of head, nystagmus.
- **Subacute sclerosing panencephalitis (SSPE):** Progressive dementia, spasticity, seizures (especially myoclonic), electroencephalography (EEG) showing burst-suppression pattern; measles antibodies in cerebrospinal fluid (CSF); supposed to be secondary to an old attack of measles.
- **Tangier disease:** Large lobulated tonsils with red, orange or yellowish banding, hepatosplenomegaly, lymphadenopathy, peripheral neuropathy, loss of pain and temperature sensation; abnormally low plasma cholesterol and nearly absent apolipoproteins.
- **TAR syndrome:** Thrombocytopenia with absent radius, autosomal recessive.
- **Three-M syndrome:** Prenatal growth deficiency, severe postnatal growth deficiency with weight below third centile for age, dolichocephaly, frontal bossing, triangular shaped face, malar hypoplasia, short nose with anteverted nares, short neck with

prominent trapezius muscles, short thorax with pectus excavatum/carinatum, mild mental deficiency.

- **Trisomy 8:** Mild to severe mental deficiency, short to tall stature, prominent forehead, strabismus, hypertelorism, micrognathia, everted lower lip, cleft palate, high arched palate, prominent ears.
- **Turner syndrome:**
 - **At birth:** Characteristic edema of dorsa of hands and feet, loose skin folds at nape of neck, LBW, low length.
 - **In childhood:** Webbing of neck, low posterior hairline, small mandible, prominent ears, epicanthal folds, high-arched palate, broad chest, cubitus valgus, hyperconvex fingernails, short stature.
 - **In adolescents:** Sexual infantilism, pigmented nevi, CVS malformations, genitourinary malformations, sensorineural hearing deficit, inflammatory bowel disease and recurrent gastro intestinal (GI) bleeding from telangiectasia become pronounced.
- **Waardenburg syndrome:** Lateral displacement of the inner canthi, prominence of root of the nose, hyperplasia of the medial portion of the eyebrows, heterochromic iris, white forelock or early graying, congenital sensorineural deafness; autosomal recessive dominance.
- **Wilms tumor, aniridia, genitourinary anomalies (WAGR) syndrome (Aniridia Wilms tumor association):** Moderate to severe mental deficiency, microcephaly, growth retardation, prominent lips, micrognathia, aniridia, congenital cataracts, ptosis, cryptorchidism, Wilms tumor.
- **WDHA syndrome:** Watery diarrhea, hypokalemia, acidosis; associated with a non B cell tumor (VIPoma) of pancreas.
- **Weber-Christian syndrome:** Recurrent episodes of fever nonsuppurative nodules in the subcutaneous tissues.
- **Williams' syndrome:** Supravalvular aortic stenosis, mental retardation, elfin facies (broad forehead, flat nose, long upper lip, rounded cheeks, hypertelorism); associated with idiopathic hypercalcemia of infancy.
- **Wilson-Mikity syndrome:** LBW, prematurity, severe apnea on day 2–5, atelectasis, reduced functional residual capacity needing therapy with continuous positive airway pressure (CPAP) or mechanical ventilation.
- **Wiskott-Aldrich syndrome:** Eczema, thrombocytopenic hemorrhage, increased vulnerability to infections due to immunodeficiency; X-linked recessive trait.
- **Wolff-Parkinson-White (WPW) syndrome:** Short PR interval, slow uptake of QRS (delta wave). May be associated with Ebstein anomaly, corrected TGV. Mostly present in normal heart.
- **Wolfram syndrome:** Insulin dependent diabetes mellitus (IDDM), optic atrophy, deafness, neurogenic bladder; autosomal recessive inheritance.
- **Wolman disease:** FTT, vomiting, diarrhea, organomegaly, adrenal calcification, leukocyte acid lipase absent; autosomal recessive.
- **Wooly hair disease:** Characteristically curly abnormal hair at birth with—(1) other ectodermal structures and hair color are normal (autosomal dominant form); (2) scalp hair of bleached appearance and body hair short and pale (autosomal recessive form); and (3) only a portion of scalp hair is fine and light-colored and shows poor growth (wooly hair nevus).
- **X-linked severe combined immunodeficiency syndrome (X-SCID):** The infant has point or deletional mutations in IL-2R, genetic defect affects B and NK-lineage cells as also T cells.
- **Yeast syndrome:** Fatigue, depression, anorexia, constipation, diarrhea and other GI complaints, lack of concentration. It is believed by some to be related to candida infection.
- **Yellow nail syndrome:** Pleural effusion, lymphedema, discolored nails; sometimes bronchiectasis. It is related to pulmonary circulation.
- **Young syndrome:** Sinusitis, bronchiectasis, azoospermia; rarely clubbing.
- **Zellweger syndrome (cerebrohepato renal syndrome):** Hypotonia, flat facies with high forehead, LBW, jaundice developing in first few days or weeks, psychomotor development delayed; death usually occurs by sixth months of age.
- **Zellweger-like syndrome:** Physical findings resembling Zellweger syndrome plus multiple peroxisomal enzyme deficiencies. Hepatic peroxisomes have normal function.
- **Zinsser-Cole-Engman syndrome (congenital dyskeratosis):** Nail atrophy, poikiloderma-like skin changes with grayish-brown pigmentation and telangiectasis; hyperhidrosis and hyperkeratosis of palms and soles; acrocyanosis and bullae over hands and feet; stomatitis and glossitis; blepharitis, ectropion and watering of eyes; scanty hair; hypoplastic anemia; squamous-cell carcinoma and hematologic defects may prove fatal; X-linked inheritance, affecting only males.
- **Zollinger-Ellison syndrome:** Peptic ulceration, hypertrophy of gastric mucosa and excessive acid secretion due to non-beta-islet cell adenoma.

Multiple Choice Questions

- Which of the following is not a components of Albright syndrome?
 - Tall stature
 - Advanced bone age
 - Precocious puberty
 - Skin pigmentation
 - Areas of osseous rarefaction resembling cysts
- Conditions that may cause Alice in Wonderland syndrome include each of the following, except:
 - Epstein-Barr virus infection
 - Epilepsy
 - Migraine
 - Schizophrenia
 - Nifedipine
- Epicanthal fold is a feature of:
 - Down syndrome
 - Lazy leukocyte syndrome
 - Sjogren syndrome
 - Progeria
 - Menkes kinky hair disease
- Wolf-Parkinson-White syndrome with short PR interval and slow uptake of QRS (delta wave) may be present in the following situations, except (2 entries):
 - Normal heart
 - Ebstein anomaly
 - Corrected transposition of great vessels
 - Tetralogy of Fallot
 - Dilated cardiomyopathy
- Supravalvular aortic stenosis is a feature of:
 - Turner syndrome
 - Kartagener's syndrome
 - William syndrome
 - Prader-Willi syndrome
 - Fetal-alcohol syndrome

Answers

1. A 2. E 3. A 4. D, E 5. C

FURTHER READING

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SECTION 10

Pediatric Drug Dosages

Section Outline

52. Pediatric Drug Dosages

- **Abacavir (Abamune):** 8 mg/kg twice daily (orally {O}) for children aged 3 months–12 years of age with a maximum dose of 300 mg.
- **Acetaminophen (Calpol, Crocin, Metacin):** 40 to 60 mg/kg/day (O) in 4 divided doses. Single dose 15 mg/kg (O). Intramuscular (IM) dose 5 mg/kg, rectal 15 mg/kg/dose.
- **Acetazolamide (Diamox):** 8 to 30 mg/kg/day (O) in 3 to 4 divided doses in epilepsy, cerebral edema and glaucoma; 5 mg/kg/day as a diuretic in congestive heart failure (CHF), 20–100 mg/kg/day, 8 hourly (O) for hydrocephalus.
- **Acetylsalicylic acid (Aspirin):** 65 mg/kg/day (O) in divided dose as an antipyretic; 65 mg/year of age/dose (O) as analgesic; 65 to 130 mg/kg/day (O) in divided dose for rheumatic fever; 30–50 mg/kg/day (O) 6–8 hourly till child becomes afebrile for Kawasaki disease.
- **Actinomycin D:** 15 µg/kg/day (intravenous {IV}) for 5 days only.
- **Adrenocorticotrophic hormone (ACTH):** 1.8 units/kg/day (subcutaneous {SC}, intramuscular {IM}, IV); 30–40 units (SC, IM) for 4 weeks in infantile spasms/ West syndrome.
- **Adenosine:** 0.05 to 0.25 g/kg dose (IV) every 2 minutes by IV push method.
- **Acyclovir (Zovirax):** Topical—5% ointment for genital, labial and corneal herpes. Oral—high dose of 800 mg to low dose of 200 mg 5 times daily for 5 days in herpes simplex and varicella (chickenpox). IV 5 to 10 mg/kg/dose every 8 hour in neonatal herpes, varicella pneumonia and immunocompromised states with superadded varicella or herpes simplex for 10 days.
- **Adrenaline (Epinephrine, 1 in 1,000):** 0.01 mL/kg/dose (SC) with a maximum of 0.6 mL/dose. Repeat every 10 to 20 minutes for 3 to 4 times or every 3 hours prn.
- **Albendazole (Alminth, Zentel):** 200 mg for up to 2 years, 400 mg beyond 2 years. Single dose suffices for most helminths except *Strongyloides stercoralis* and tapeworms which need 3 days course. *Giardia lamblia* needs a 5 days course. For neurocysticercosis give 15 mg/kg/day in 2 divided doses for around 7 days (though some still prefer a 28 days course) with corticosteroids for 5 days
- **Albumin:** 2 mL/kg/dose (IV)/0.5–1g/kg/dose IV.
- **Albuterol:** 0.1 to 2 mg/kg/day (O) in 3 to 4 divided doses.
- **Allopurinol (Zyloric, Ciploric):** 10 to 20 mg/kg/day in 3 divided doses.
- **Alprostadil:** 0.05 to 0.1 µg/kg/min as a continuous IV infusion may be gradually increased to a maximum of 0.4 µg/kg/minimum depending on the response.
- **Aluminium hydroxide (Aludrox):** For treatment of peptic ulcer 5 to 15 mL/dose every 3 to 6 hours. For prophylaxis of gastrointestinal bleed 2 to 5 mL every 1 to 2 hour.
- **Amikacin (Mikacin, Ivimicin):** Neonates above 7 days—30 mg/kg/day in 3 divided doses. Neonates under 7 days—15 mg (weight below 2 kg) and 10 mg (weight above 2 kg)/kg/day in 2 divided doses.
- **Aminophylline:** 4 to 6 mg/kg/dose (IV, IM) 10 mg/kg/dose (O). Repeat every 8 hours. For apnea in preterms, 5mg/kg (IV) loading dose followed by 2 mg/kg 8 hourly.
- **Aminosidine sulfate (Garamicina):** 10 to 20 mg/kg/day (IM) in 2 to 3 divided doses.
- **Amitriptyline (Tryptanol, Sarotena):** 1.5 mg/kg/day (O).
- **Amodiaquin (Camoquin):** 20 mg/kg/day (O) as single dose. If maintenance dose needed, give 8 mg/kg/day.
- **Amoxycillin (Amoxyl, Lamoxy, Novomax, Flemipen, Comoxyl, Wymox):** 20 to 40 mg/kg/day in 3 divided doses. 50 to 100 mg/kg/day (IM, IV) in 3 divided doses in serious infections. For meningitis 200 to 400 mg/kg/day (IV).
- **Amoxycillin with clavulanic acid (Augmentin):** See Amoxycillin for calculation of dose.
- **Ampicillin (Roscollin, Campicillin):** 50 to 400 mg/kg/day (O, IM, IV) in 4 divided dose.
- **Anti-Rhesus (Rh)-D immunoglobulin (Ig):** For antenatal prophylaxis give 300 µg IM at 28 weeks (1st) 2nd 34 weeks or single dose 72 hours within delivery. In twin pregnancy give double dose. In case of abortion/evecuation/amniocentesis/cordocentesis/ antepartum hemorrhage (APH) give 150 µg IM, if procedure is done before 12 weeks of gestation.
- **Artemether:** Severe falciparum malaria 3.2 mg/kg (IM) on first day, 1.6mg/kg/daily for next 5 days (total 9.6 mg/kg) shift to oral as soon as possible.
- **Artesunate:** Severe falciparum malaria 2.4 mg/kg/dose (IV/IM) 0, 12, 24 hours followed by oral dose (OD) for 7 days.
- **Ascorbic acid (vitamin C):** 100 to 500 mg/day (O).
- **Astemizole (Sterniz):** 0.2 mg/kg (O) as a single dose as first thing in the on empty stomach. Contraindicated in porphyria, long QT, epilepsy.

- 890 ■ Atenolol:** 0.8 to 1.5 mg/kg/day to a maximum of 2 mg/kg/day orally.
- **Atropine sulfate:** 0.01 mg/kg/dose (O/SC) with a maximum of 0.4 mg/dose. Repeat every 4 to 6 hours prn; 0.02 to 0.05 mg/kg/dose as antidote to organophosphorus poisoning.
 - **Atropine sulphate:** 0.02 to 0.05 mg/kg/dose as antidote to organophosphorus poisoning.
 - **Azathioprine (Imuran):** Start with 3–5 mg/kg/day maintenance 1 to 3 mg/kg/day (O).
 - **Azithromycin dihydrate (Azithral):** 10 mg/kg (O) once a day for 3 days.
 - **British anti-Lewisite (Dimercaprol):** 2.5 mg/kg/dose (IM) 1st, 2nd and 3rd dose every 4, 6 and 12 hours respectively. Follow by a single daily injection for the subsequent 10 days.
 - **Beclomethasone:** 1 to 2 inhalations 2 to 4 times a day to a maximum of 10 puffs (42 µgm/puff).
 - **Beractant (lung surfactant):** 4 mL/kg via endotracheal tube (slow infusion).
 - **Betamethasone dipropionate (Vanceryl inhaler):** 1–2 inhalations 6 to 8 hourly (each inhalation providing about 50 mcg betamethasone).
 - **Bephenium hydroxynaphthoate (Alcopar):** 2.5 g for children under 5 years, 5 g for children above 5 years (O) on empty stomach.
 - **Benzathine penicillin:** < 27 kg 6 lakh units, > 27 kg (IM) every 3 weeks for secondary prophylaxis in rheumatic fever. Congenital syphilis—50,000 units/kg/dose (IM) once a week for 3 weeks.
 - **Budesonide:** Pulmicort inhaler 1 to 2 puffs a day for children over 6 years.
 - **Busulfan (Myleran):** 0.006 mg/kg/day (O).
 - **Calcitriol:** 0.01–0.05 mcg/kg/day.
 - **Calcium gluconate:** 500 mg/kg/day (O) as 5 to 10% solution; 200 mg/kg/dose (IV) with a maximum of 2 g.
 - **Calcium lactate:** 500 mg/kg/day in 3 to 6 divided doses.
 - **Captopril (Aceten, Acezide, Aceten):** 0.1–0.4 mg/kg/day in 2 to 4 divided doses. Increase slowly to a maximum of 2.0 mg/kg/day.
 - **Carbamazepine (Tegretol, Mezetol):** 10 to 20 mg/kg/day (O).
 - **Carbenicillin (Carbelin):** 50 to 400 mg/kg/day (IM, IV) in 4 to 6 divided doses.
 - **Carbimazole (Neo-mercazole):** 1–2 mg/kg/day (O) in 3 divided doses.
 - **Cefaclor (Keflor):** 20 to 40 mg/kg/day (O) in 3 divided doses.
 - **Cefadroxil (Cefadrox, Lydroxil):** 30 mg/kg/day in 2 divided doses.
 - **Cefotaxime (Claforan, Omnatax):** 100 to 200 mg/kg (IM, IV) in 2 to 4 divided doses.
 - **Cefazolin (Cefamezin, Cefazin, Orizolin):** 25 to 50 mg/kg/day (IM, IV) in 2 to 4 divided doses.
 - **Cefixime:** 8 mg/kg (O) in 2 divided doses.
 - **Cefoperazone sodium:** 50 to 200 mg/kg/day (IM/IV) in 2 to 3 divided doses.
 - **Cefpodoxime proxetil:** 8 to 10 mg/kg/day (O) in 2 divided doses.
 - **Ceftazidime (Fortum):** Under 2 months—25 to 60 mg/kg/day (IM, IV) in 2 divided doses. Above 2 months—30 to 100 mg/kg/day (IM, IV) in 2 or 3 divided doses.
 - **Ceftibuten (Procadex):** 9 mg/kg once a day.
 - **Ceftriaxone (Monocef):** 20 to 80 mg/kg/day (IM) in 1 or 2 doses.
 - **Cefuroxime axetil (Altacef, Cefogen):** 25–50 mg/kg/day (IM, IV) in 2 divided doses.
 - **Cephalexin (Sepexin, Spolidex):** 25 to 100 mg/kg/day (O) in 4 divided doses.
 - **Cephaloridine (Sporidine, Ceporan):** 15 to 30 mg/kg/day (IM, IV) in 2 to 3 divided doses. In severe infections, especially with Gram-positive organisms, dose is 40 to 60 mg/kg/day; 1 mg/kg/dose intrathecal (IT).
 - **Cetirizine (Alerid):** 2–6 years 2.5 to 5 mg, 6–12 years 5 to 10 mg (O) as a single dose; 0.2 mg/kg/day (O) as a single dose.
 - **Chloral hydrate:** 5 mg/kg/dose (O or rectally) for sedation; 50 mg/kg/day for hypnosis with a maximum of 2 g.
 - **Chlorambucil (Leukeran):** 0.1 to 0.2 mg/kg/day (O).
 - **Chloramphenicol (Chloromycetin):** 50 to 100 mg/kg/day (O, IM, IV) in divided dose. The dose in newborn, especially in first two weeks of life, should be 25 mg/kg/day.
 - **Chlordiazepoxide (Librium):** 0.5 mg/kg/day (O).
 - **Chloroquine (Nivaquine, Lariago, Emquin):** 10 mg/kg/day (O); 5 mg/kg (IM).
 - **Chlorpromazine (Largactil):** 0.5 to 1 mg/kg/dose (O or IM), 2 to 3 mg/kg/day in 4 to 6 divided doses.
 - **Chlorothiazide (Diuril):** 7 to 40 mg/kg/day (O or IV) in 2 divided doses.
 - **Chlorpheniramine:** 0.35 mg/kg/day (O or SC) in 4 divided doses.
 - **Cimetidine:** 20 to 40 mg/kg/day in divided doses.
 - **Ciprofloxacin:** 20 to 30 mg/kg/day (O) and 10 to 20 mg/kg/day (IV) in 2 divided doses.
 - **Cisapride:** 0.8 mg/kg/day (O) in 4 divided doses.
 - **Clarithromycin:** 10 to 15 mg/kg/day in 2 divided doses.
 - **Clindamycin (Dalacin, Dalcop):** <7 days and weight <2000 g 10 mg/kg/day in 3 divided doses, <7 days and weight >2000 g 15 mg/kg/day in 3 divided doses, children 20 to 45 mg/kg/day in 3 to 4 divided doses.
 - **Clobazam:** 0.1 mg/kg/day initial dose. Usual maintenance dose 0.3 to 1 mg/kg/day 12 hourly.
 - **Clonazepam (Rivotril, Klonopin):** 0.01 to 0.03 mg/kg/day to start with. Thereafter, 0.3 mg/kg/day every 8 hours, after building up dose by increments of 0.25 mg every 3 days.
 - **Clonidine hydrochloride (Catapres, Arkamin):** 5 to 10 mcg/kg/day.
 - **Cloxacillin (Klox):** 50 to 200 mg/kg/day (O or IM) in 4 divided doses.
 - **Co-amoxiclav (Augmentin):** See amoxycillin with clavulanic acid.

- **Codeine phosphate/sulfate:** 1 to 1.5 mg/kg/day for suppression of cough; 3 mg/kg/day for sedation or as analgesic.
- **Colistin (Walamycin):** 5 to 8 mg/kg/day (O) in divided doses.
- **Cortisone acetate (Cortin):** 2.5 to 10 mg/kg/day (O) in 3 divided doses. IM and IV dose is 1/2 of this.
- **Co-trimoxazole (Septran, Oripriam, Bactrim, Supristal, Synastat):** 4 to 10 mg/kg/day in terms of trimethoprim (O, IV) in 2 divided doses.
- **Cromoglycate sodium (Cromal 5, Ifiral):** 20 mg every 6 hours by inhalation.
- **Cyanocobalamin:** 30 to 50 µg/day to a total dose of 1000 to 5000 µg and then 100 µg every month in pernicious anemia.
- **Cyclizine:** 6 to 12 years 25 mg/dose (O) upto 3 times/day as needed.
- **Cyclophosphamide (Endoxan):** 2 to 3 mg/kg/day (O or IV) in divided doses or total of 7 days dose once in a week. For resistant neoplasm, use 4 to 8 mg/kg/day.
- **Cycloserine:** 15 to 25 mg/kg/day (O) in 3 to 4 divided doses.
- **Cyproheptadine (Peritol, Ciplactin):** 0.25 mg/kg/day (O) in 3 to 4 divided doses.
- **Dantrolene:** Initially 0.5 mg/kg/dose twice a day. Build up dose in increments until desired result is obtained. Malignant hypothermia—1g/kg, IV.
- **Dapsone:** Leprosy 1–2 mg/kg/day as single dose in combination with rifampicin. Blistering skin condition 500 µg/kg/day.
- **Daunorubicin:** 0.5 to 1 mg/kg at one day or more intervals; 2 mg/kg at 4 days or more intervals; 2.5 to 3 mg/kg at 7 to 14 days intervals, 25–45 mg/sqm on day 1 of every week for 4 cycles.
- **Deferiprone (Oral chelating agent):** 100 mg/kg/day (O), 250 mg (TID).
- **Deferoxamine (Desferal):** 30 to 70 mg/kg (SC infusion, administered by a special pump) over 5 to 8 hours 6 times a week. For high dose IV therapy, 6 to 12 g/day.
- **Desloratadine:** 2–5 years, 1.2 mg OD, 6–11 years, 2.5 mg OD, 12–18 years, 5 mg OD (O).
- **Desmopressin acetate (DDAVP):** 5 to 30 mcg/day in 1 or 2 divided doses as nasal insufflation.
- **Dexamethasone:** 0.25 to 0.6 mg/kg/day in 3 divided doses.
- **Dextromethorphan:** 1 mg/kg/day in 2 to 3 divided doses (before food).
- **Dextropropoxyphene:** 2 to 4 mg/kg/day in divided doses.
- **Diazepam (Calmose, Valium):** 0.1 to 0.5 mg/kg/dose (IM, IV) or 1 mg/year of age to a maximum 10 mg; 0.1 to 0.8 mg/kg/day (O) in 3 to 4 divided doses.
- **Diazoxide (Hyperstat):** 5 mg/kg (IV) single dose.
- **Dichlorophen (Anthiphen):** 2 to 4 g daily for 2 days.
- **Dicyclomine (Colimex):** 5 mg/dose in infants > 6 months, 10 mg/dose in children, 40 mg/dose in adolescents.
- **Diethylcarbamazine (Hetrazan):** 15 mg/kg/day (O) as single daily dose for 4 days in ascariasis; 10 to 12 mg/kg/day (O) in divided doses for 5 days, or 6 mg/kg/day (O) in divided doses for 5 days in filariasis and tropical eosinophilia.
- **Digoxin:** See Chapter 16 (Fluid, Electrolyte and Acid-Base Balance and Disturbances).
- **Diiodohydroxyquin (Diodoquin):** 40 mg/kg/day (O) in 2 to 3 divided doses.
- **Diloxanide furoate (Furamide):** 20 mg/kg/day (O) for 10 days.
- **Diltiazem:** 1.5 to 2 mg/kg/day (O) in 3 to 4 divided doses; 12–18 years 30–60 mg/dose 2–3 times daily.
- **Diphenoxylate hydrochloride (Lomotil):** 0.3 mg/kg/day (O) in divided doses.
- **Diphenhydramine (Benadryl):** 4 to 6 mg/kg/day (O) in 3 to 4 divided doses. For its use as antidote in phenothiazine toxicity See Chapter 32 (Pediatric Hematology).
- **Diphenylhydantoin sodium (Dilantin):** 3 to 8 mg/kg/day (O) as single dose or in 2 divided doses; 10 to 15 mg/kg (IV, IM).
- **Domperidone (Gastractiv, Domperon):** 0.2 to 0.4 mg/kg at 4 to 8 hours intervals.
- **Dopamine hydrochloride:** Start with 0.002 to 0.005 mg/kg/minute. If needed, increase by increments of 0.005 mg/kg/minute upto 0.05 mg/kg/minute.
- **Doxorubicin (Adriamycin):** 1.2 to 2.4 mg/kg/dose (IV) every 3 weeks.
- **Doxycycline:** 5 mg/kg/day (O) in 2 divided doses in first day. Then 2.5 mg/kg/day as a single daily dose.
- **Doxapram:** 2.5 mg/kg over 5–10 minimum IV infusion.
- **Ebastine:** > 6 years 5 mg OD.
- **Enalapril:** 0.1 to 0.5 mg/kg/day (O) in 1 to 2 divided doses. 5 to 10 µg/kg/day (IV) in 1 to 2 divided doses.
- **Ephedrine sulfate:** 3 mg/kg/day (O) in 4 to 6 divided doses. 1–2 drops intranasal.
- **Epinephrine:** See adrenaline.
- **Ergocalciferol:** 75 to 125 µg/day in rickets.
- **Erythromycin (Erythrocin, E-Mycin):** 40 to 50 mg/kg/day (O). The dose for newborn is 25 to 40 mg/kg/day (O).
- **Erythropoietin:** 25–100 units/kg (SC/IV) 3 times in a week, monitor hemoglobin (Hb).
- **Etanercept:** 400 µg/kg (SC) twice weekly.
- **Ethacrynic acid:** 25 mg/dose (O); 0.5 to 1.0 mg/kg/dose (IV).
- **Ethambutol:** 15 to 25 mg/kg/day (O) in a single dose.
- **Ethionamide:** 10 to 20 mg/kg/day, with a maximum of 750 mg, in divided doses.
- **Ethosuximide (Zarontin):** <6 years—250 mg/day (O); >6 years—500 mg/day (O), in 2 divided doses; or 15 to 25 mg/kg/day (O).
- **Famotidine:** 0.4 mg/kg/day.
- **Fentanyl citrate:** 0.5 µg/kg/dose (IV) 1–4 hours, IV continuous infusion.
- **Ferrous sulfate (Fersolate):** 1 mg/kg/day (O) for prophylaxis; 6 mg/kg/day (O) for therapeutic use (elemental iron).
- **Fluconazole:** 3–6 mg/kg/day once daily, invasive candidiasis—6–12 mg/kg/day, 28 days.

- 892 ■ Flumazenil:** IV 0.1 mg, 0.2 mg, 0.3 mg, 0.5 mg at 1 minute interval until effect is achieved.
- **Fluticasone:** Rota disk dose 50 to 1000 µg twice depending upon asthma severity and need for systemic corticosteroids; 2–4 years—50–100 µg, 4–16 years—50–200 µg, >16 years—100 µg–1 mg twice daily.
 - **Folic acid:** 5 to 20 mg/day (O), 1 mg/day (IM).
 - **Foscarnet:** Cytomegalovirus (CMV) retinitis in AIDS patient 180 mg/kg/day q8 hour IV slow infusion over 1 hour for 21 days, then 90–120 mg/kg once daily as maintenance.
 - **Fosphenytoin:** Loading dose 15–20 mg/kg/day (IV/IM) maximum infusion rate—3 mg/kg/minutes.
 - **Furosemide (Lasix):** 1 to 3 mg/kg/dose (O), 0.5 to 1.5 mg/kg/dose (IM).
 - **Furazolidone (Furoxone):** 8 mg/kg/day in 3 to 4 doses.
 - **Gelatin:** In hypovolemic shock, 10–20 mL/kg bolus rapidly. In trauma, 40 mL/kg.
 - **Gentamicin (Garamycin):** 3 to 5 mg/kg/day (IM/IV) in first week of life, later up to 7.5 mg/kg/day in divided doses.
 - **Griseofulvin:** 10 to 20 mg/kg/day as a single dose in divided doses.
 - **Growth hormone:** 0.5–1 unit/kg once a week (spinal cord independence measure {SCIM}) alternatively, 0.07–0.14 unit/kg OD.
 - **Guanethidine sulfate (Ismelin):** 0.2 mg/kg/day (O) in 1 or 2 divided doses.
 - **Glucagon:** Hypoglycemia (IM/SC/IV) newborn 20 µg/kg, 25 kg–500 µg/kg, 25 kg–500 µg–1 mg as single dose. PO 25% glucose IV if no response.
 - **Glutamine:** 250–500 mg/kg/day of L-glutamine have been used.
 - **Glutaraldehyde:** Topical removed dead skin by rubbing, apply twice daily, each drop to dry before next.
 - **Glycerol:** Rectal less than 1 year—1 gm, 1–12 years—2 gms, 12–18 years—4 gms.
 - **Glyceryl trinitrate:** IV 0.5 µg/kg/minimum IV maximum upto 10 µg/kg/minimum monitor BP (blood pressure) and heart rate (HR).
 - **Glycerine:** 5–0 mg/kg/dose 3 times daily maximum 200 mg/kg TID.
 - **Glycopyrrolate:** IM/IV premedication/intraoperative, 4–8 µg/kg as single dose.
 - **Gonadotropin-releasing hormone (GnRH):** IV/SC 2.5 µg/kg (maximum–100 µg) as single dose.
 - **Goserelin:** 3.6 mg every 4 weeks/10.8 mg every 12 weeks.
 - **Granisetron:** Oral—1 month–12 years, 20 µg/kg/dose to a maximum of 1 mg.
 - **Haloperidol (Serenace):** 0.05 mg/kg/day (O), 25–50 µg/kg/day in Tourette syndrome.
 - **Heparin:** 50 units/kg followed by 100 units/kg to be added to IV drip, 15–35 units/kg/hour, IV as maintenance.
 - **Human albumin solution:** Hypovolemic shock—10–20 mL/kg bolus, trauma—40 mg/kg.
 - **Hydralazine (Apresoline):** 0.75 mg/kg/day (O) in 4–6 divided doses.
 - **Hydrochlorothiazide (Esidrex):** One-tenth of chlorothiazide dose.
 - **Hydrocortisone:** In shock 50 mg/kg/dose IV every 4 hourly. Anti-inflammatory dose 1 to 5 mg/kg/day in 1 to 2 divided doses (IV, IM) and 2.5 to 10 mg/kg/day divided every 6 to 8 hourly (O).
 - **Hydroxyzine:** 6 months–6 years—5–15 mg, 7–12 years—10–15 mg, 12–18 years—25 mg at bed time.
 - **Hyoscine butylbromide:** 2–12 years 10 µg/kg, 12–18 years 300 µg 4 times daily.
 - **Ibuprofen (Brufen):** 20 mg/kg/day in 3 divided doses.
 - **Ifosfamide:** IV 1200–1800 mg/m² as a single IV-infusion.
 - **Iloprost:** 12–18 years IV infusion start with 0.5 mg/kg/minimum over 6 hours daily once for 3–5 consecutive days followed by maintenance 1–2 mg/min/day.
 - **Imipramine (Depsonil):** 1.5 mg/kg/day (O) in 3 to 4 divided doses.
 - **Isonicotinylhydrazide (INH):** 5 to 20 mg/kg/day (O) with a maximum of 300 mg/day.
 - **Imatinib mesylate:** 260 mg and 350 mg/m² equivalent to the adult dose of 400 mg chronic phase and 600 mg/day accelerated/blast phase crisis respectively.
 - **Imiglucerase:** IV infusion type-1 disease 60 units/kg given every 2 weeks.
 - **Indomethacin (Indocap, Ceplacid, Idicid):** 1 to 3 mg/kg/day (O) in 3 to 4 divided doses for anti-inflammatory/analgesic effect. For closure of patent ductus arteriosus (PDA) <48 hour—0.2 mg/kg for 1 dose, then 2 doses of 0.1 mg/kg; 2 to 7 days—3 doses of 0.2 µg/kg; > 7 days—0.2 mg/kg once, then 2 doses of 0.25 mg/kg (IV).
 - **Insulin:** 0.1 unit/kg/hour (IV infusion) of soluble; 0.5 unit/kg/day in 3 divided doses.
 - **Infliximab:** Severe active Crohn disease—IV infusion 5 mg/kg, single dose over 2 hours. If recurrence occurs, readminister within 14 weeks after first dose.
 - **Interferon alpha:** SC less than 12 years–3 million units/m², more than 12 years—3–10 million units/m² usually 3 times/week.
 - **Interferon gamma-Ib:** Surface area < 0.5m²—1.5 µg/kg/dose, surface area >0.5m²—50 µg/kg/dose (SC) 3 times a week.
 - **Iron-Dextran (Imferon):** See Chapter 22 (Helminthic Infections and Infestations).
 - **Iron sorbitol (Jectofer):** 1.5 mg (0.33 mL) kg/dose (IM).
 - **Isoniazid:** See INH.
 - **Isoproterenol hydrochloride:** 2 to 10 mg/dose sublingually thrice daily.
 - **Ivermectin:** 0.15 mg/kg as single dose; repeat every 6–8 months.
 - **Kanamycin (Kancin):** 10 to 15 mg/kg/day (IM).
 - **Ketotifen:** 0.25 to 0.5 mg (O) BD, adolescents—1–2 mg OD with food, not recommended below 2 years.

- **Ketamine:** <12 years, 1–2 mg/kg and 12–18 years, 1–4.5 mg/kg (IV) as induction followed by maintenance ½ of induction.
- **Ketoconazole:** 3.3–6.6/kg (O) once daily.
- **Lactulose (Livoluk):** Infants 2.5 to 10 mL/day in 3 to 4 divided doses, children 40 to 90 mL/day in 3 to 4 divided doses (O, PR), hepatic encephalopathy—30 to 50 mL TID.
- **Labetalol:** Oral stat 4 mg/kg/24 hours 2 divided doses with a maximum of 40 mg/kg/24 hours.
- **Lamivudine:** Adolescents—300 mg/day.
- **Lamotrigine:** 5–15 mg/kg/day.
- **Lansoprazole:** Gastroesophageal reflux disease, acid dyspepsia, children <30 kg—0.5–1 mg/kg, children >30 kg—15–30 mg once daily.
- **L-Asparaginase (Leunase):** 50 to 200 units/kg/day (IV infusion).
- **Leuporelin:** 3.75 mg every 4 weeks/11.25 mg depot preparation every 12 weeks.
- **Levamisole (Dewormis):** 5 mg/kg on alternate days.
- **Levothyroxine:** See thyroxine.
- **Lincomycin Hcl (Lincocin):** 30 mg/kg/day (O), 10 mg/kg/day (IM) 10 to 20 mg/kg/day (IV) in 2 to 3 divided doses.
- **Linezolid:** 400–600 mg every 12 hourly.
- **Liquid paraffin:** 3–12 years—0.5–1 mg/kg, 12–18 years—10–30 mL once daily.
- **Lithium:** 12–18 years—200–800 mg/doses 3 times daily.
- **Loratadine:** <6 years—5 mg once daily, >6 years—10 mg once daily.
- **Loperamide (Lopamide, Imodium, Peloperin):** 0.3 mg/kg/day (O) or 0.1 mg/kg/dose (O).
- **Loratadine (Loridin):** 5 mg/day for weight upto 30 kg 10 mg/day for weight >30 kg.
- **Lorazepam (Larpose):** Sedation 0.05 mg/kg/dose (O), status epilepticus 0.05 mg/kg/dose (IV, IM), to be repeated after 15 to 20 minutes if indicated.
- **Magnesium hydroxide (Milk of Magnesia):** 0.5 mg/kg/day (O).
- **Magnesium sulfate:** 0.1 to 0.4 mg/kg/dose (IM) as anticonvulsant, neonatal hypocalcemia IM- 100 mg/kg/dose.
- **Mannitol:** For cerebral edema 2 g (10 mL)/kg as 20% solution given in 2 to 6 hours (IV). For oliguria/anuria 0.2 g, i.e. 1 mL/kg (IV) single dose given in 3 to 5 minutes. Peripheral edema/ascites-IV infusion 1–2 g/kg 2–6 hours.
- **Mebendazole (Wormin, Mebex, Pentelamin):** 100 mg twice daily for 3 days (O). For tapeworms (*Taenia saginata*, *Taenia solium*), the dose is double, i.e. 200 mg. On the contrary, a single dose of 100 mg, given only once, suffices in case of pinworm infestation.
- **Mefenamicacid (Meftal):** 6.5 mg/kg/dose (O) or 20 to 30 mg/kg/day in divided doses.
- **Mepacrine:** 5 mg/kg/day (O) in 3 divided doses for 5–7 days for giardiasis; 15 mg/kg with a maximum of 800 mg as a single dose for tapeworms.
- **Mercaptopurine (6-MP, Purinethol):** 2.5 mg/kg/day (O). **893**
- **Metakelfin:** See sulfamethoxyypyrazine.
- **Metformin:** 500–1000 mg/dose 2–3 times daily.
- **Methenamine mandelate (Mandelamine):** 50 to 100 mg/kg/day (O) in 3 divided doses.
- **Methicillin (Staphcillin):** Newborn—100 mg/kg/day (IM/IV). Others—100 to 400 mg/kg/day (IM/IV) in 4 to 6 divided doses.
- **Methotrexate:** 0.12 mg/day (O), 0.25 to 0.5 mg/kg/day (IT), 3 to 5 mg/kg (IV) as single dose every other week.
- **Methyldopa (Aldomet):** 10 mg/kg/day (O) in 4 divided doses, increasing at 2 days or more intervals to as high as 65 mg/kg/day if needed.
- **Methylprednisolone:** 0.4–1.7 mg/kg/day (IM, IV). Pulses—30 mg/kg/day for 3–5 days. Shock and other emergencies—30 mg/kg/dose over 10–20 minutes; may need repeat doses 4–6 hourly.
- **Metoclopramide (Perinorm, Maxeran, Reglan):** 0.5 mg/kg/day (O, IM, IV) in 3 divided doses.
- **Metoprolol:** 1 to 5 mg/kg/day in 2 to 3 divided doses.
- **Metronidazole (Flagyl, Metrogyl):** 10–20 mg/kg/day (O) for 5 to 7 days in divided doses for giardiasis, 20 to 50 mg/kg/day (O) for 10 days in divided doses for amebiasis. IV dose is 21 mg/kg/day.
- **Midazolam:** 0.15 mg/kg (IV) followed by continuous infusion of 1 to 2 µg/kg/minimum in status epilepticus.
- **Milk of Magnesia:** See magnesium hydroxide.
- **Minoxidil:** 0.2 mg/kg/day (O) as a single dose. Follow by stepwise increase to 0.25 to 1 mg/kg/day.
- **Mitomycin C:** 0.05 mg/kg/day (IV) for 5 days.
- **Morphine:** 0.1 to 0.2 mg/kg/dose (SC).
- **Moxiactum (Moxam):** Under 7 days—100 mg/kg/day in 2 divided doses. Above 7 days—150 mg/kg/day in 3 divided doses.
- **Mupirocin (Bactroban, T-Bact):** The ointment is required to be topically applied to the affected skin area (Gram-positive infections, including methicillin-resistant and beta-lactamase producing strains of staphylococcus) thrice daily.
- **Mustine Hcl:** 0.1 to 0.4 mg/kg/dose (IV) with a maximum 8 mg for 3 to 4 days.
- **Nalidixic acid (NegGram, Gramoneg):** 50 mg/kg/day (O) in 4 divided doses.
- **Naloxone:** 0.1 mg/kg/dose (IV) to maximum dose 2 mg.
- **Naproxen (Naxid, Artagen):** 10 mg/kg/day (O) in 2 divided doses.
- **Neostigmine:** Myasthenia gravis 0.01 to 0.04 mg/kg/dose (IM, IV, SC) in 5 to 10 minutes every 2 to 4 hours.
- **Netilmicin sulfate (Netromycin):** 2.5 to 3.0 mg/kg/dose (IM, IV).
- **Neomycin:** 50 to 100 mg/kg/day (O) in 3 to 4 doses.
- **Niclosamide (Yomesan, Niclosan):** 40 mg/kg (O) with a maximum of 2 g for 7 days in *Hymenolepis nana* and a single dose in *T. solium* and *T. saginata*.
- **Nifedipine (Calcigard):** 0.2 to 0.7 mg/dose (SL).
- **Nikethamide (Coramine):** 0.1 mg/kg/dose (IV, IM).

- 894 ■ Nimesulide (Nimulid, Nise):** 5 mg/kg/day (O) in 2 or 3 divided doses.
- **Nitrazepam (Nitrazet):** 0.12 to 0.2 mg/kg/day in single or 2 divided doses.
 - **Nitrofurantoin (Furadantin):** 5 to 10 mg/kg/day (O) in divided doses. Contraindicated in infants <3 months age.
 - **Nitrogen mustard (Mustargen):** 0.4 mg/kg (IV) as single dose or in 2 divided doses at intervals of 1 to 2 weeks.
 - **Nandrolone (Durabolin):** Infants—5 mg once a week or 10 mg once a fortnight (IM); children—10 to 12.5 mg once every 10 days.
 - **Norepinephrine:** 0.05 to 0.1 µg/kg/minute to maximum dose 2 µg/kg/minute.
 - **Norfloxacillin (Noroxin):** 4 to 12 mg/kg/day for 5 days for gastrointestinal (GI) infection; 7 to 21 days for urinary tract infection (UTI), in single or 2 doses. A single high dose treatment for gonorrhea suffices.
 - **Nystatin (Mycostatin):** Newborn—4 lakh units/day in divided doses (local application); children—1 to 2 million units/day in divided doses.
 - **Nitric oxide:** Delivered along with O₂ through ventilator in a dose of 5–80 parts per million (ppm), more than 33 weeks start with 20 ppm, less than 33 weeks start with 5 ppm and increase maximum to 40 ppm.
 - **Octreotide:** Varices—IV infusion 1 µg/kg/hour initially; may increase to 3 µg/kg/hour till bleeding is controlled.
 - **Ofloxacin (Tarivid):** 4 to 16 mg/kg/day as a single dose or in 2 divided doses.
 - **Olanzapine:** 12–18 years—5–20 mg once daily; usual dose 10 mg.
 - **Omeprazole (Odd):** 20 mg OD before breakfast (only for grown-ups).
 - **Orciprenaline (Alupent):** 0.02 mg/kg/dose (IM), 2–3 mg/kg/day (O) in 4 divided doses.
 - **Oxacillin (Prostaphilin):** 50 to 200 mg/kg/day in divided doses.
 - **Oxymetholone (Anadrol):** 0.1 to 0.8 mg/kg/day (O).
 - **Palivizumab:** 15 mg/kg once monthly starting just prior to the beginning of the respiratory syncytial virus (RSV) season for a total of 5 doses.
 - **Pancreatin (Pancreatic enzymes):** 300 to 600 mg with each main meal.
 - **Paracetamol (Calpol, Crocin, Metacin):** See acetaminophen.
 - **Paraldehyde:** 0.15 mL/kg/dose (O, IM, IV) 0.3 to 0.6 mL/kg/dose (rectal).
 - **Paromomycin (Humatin):** 25 to 50 mg/kg/day in 3 divided doses for 5 to 10 days.
 - **Para-amino salicylate (PAS):** 200 to 400 mg/kg/day in divided doses.
 - **Pemoline:** 1 mg/kg/day orally, as single dose each morning to maximum dose 3 mg/kg/day.
 - **Penicillamine:** Wilson disease 20 mg/kg/day in 2–4 divided doses (O), lead poisoning 25 to 40 mg/kg/day in 3–4 divided doses, cystinuria 30 mg/kg/day in 4 divided doses, rheumatoid arthritis 3 mg/kg/day (maximum 250 mg/day total dose) in 2 divided doses for 3 months with dose increase to 6 mg/kg/day (maximum 600 mg/day) according to tolerance. In adolescents, dose is 125 to 250 mg/day increased to 1 to 1.5 g/day.
 - **Penicillin:**
 - **Oral (Pentids):** 50 thousand units/kg/day in 3 to 4 divided doses.
 - **Procaine:** <4 years—2 lakh units (IM) once or twice daily, >4 years—4 lakh units (IM) once or twice daily.
 - **Crytalline:** 50 thousand to 4 lakh units/kg/day (IM or IV) in divided doses.
 - **Long acting:** See Chapter 22 (Helminthic Infections and Infestations).
 - **Pethidine:** 1 to 2 mg/kg/dose (IM).
 - **Pheniramine maleate:** 1 to 5 mg/kg/day (O, IM).
 - **Phenobarbital (Luminal):** 3 to 5 mg/kg/dose (IM) for acute attack of convulsions, 3 to 5 mg/kg/day (O) for maintenance therapy and sedation.
 - **Phenytoin:** See Diphenylhydantoin sodium.
 - **Piperazine:** 100 to 150 mg/kg (O) as a single administration for ascariasis; 50 to 75 mg/kg/day for 7 successive days for pinworm infestation.
 - **Piracetam (Neurocetam):** 40 mg/kg in divided doses (O).
 - **Piroxicam:** 0.2 to 0.3 mg/kg/day (O) to max dose 15 mg/kg/day.
 - **Potassium chloride:** 1 to 3 mEq/kg (IV) for hypokalemia, 3 to 5 mEq/kg/day (O) for advanced pediatric emergency medicine (PEM).
 - **Prazosin:** 30 µg/kg/dose, repeated after 3 hours and 6 hours till improvement.
 - **Praziquantel (PZQ):** 50 mg/kg/day (O) in 3 divided doses for 14 days for neurocysticercosis; 50 mg/kg (O) single dose once daily for tapeworms and liver fluke.
 - **Pralidoxime:** 20 to 50 mg/kg/dose (IM, IV). Repeat if needed after one hour.
 - **Prednisolone (Wysolone):** Generally 1 to 2 mg/kg/day in divided doses (O).
 - **Primaquine:** 0.3 mg (base)/kg/day (O) for 14 days. Also See Chapter 14 (Vitamins).
 - **Primidone (Mysoline):** 125 mg for under 8 years and 250 mg after 8 years, twice or thrice daily; 40 to 50 mg/kg/day in 2 to 3 divided doses.
 - **Probenecid (Procid, Benemid):** 250 mg twice daily for one week followed by 500 mg twice daily.
 - **Prochlorperazine (Stemetil):** 0.5 mg/kg/day (O) in divided doses.
 - **Promethazine (Phenergan):** 0.5 mg/kg/dose (O, IM).
 - **Propranolol (Ciplar, Inderal):** 0.15 to 0.25 mg/kg/dose (IV) for cyanotic spells; 0.5 to 1 mg/kg/day (O) in divided doses for arrhythmias. For hypertension, dose is far higher.
 - **Pseudoephedrine hydrochloride (Sudafed):** 3 to 5 mg/kg/day in 4 divided doses.
 - **Pyrantel (Nemocid, Antiminth):** 10 mg/kg (O) as a single dose.

- **Pyribenzamine:** 5 mg/kg/day (O) in 4 to 6 divided doses.
- **Pyridoxine:** 50 to 100 mg/day (O, IM, IV) for pyridoxine dependence.
- **Pyrazinamide:** 15 to 40 mg/kg/day to maximum dose 2 g/day.
- **Pyrvinium (Vanquin):** 5 mg/kg/day (O).
- **Quinine:** 25 mg/kg/day in 3 divided doses (O) for 10 to 14 days; 10 mg/kg/dose (IV) by slow infusion over 1 to 2 hours, to be repeated at intervals of 12 hours till clinical response occurs.
- **Ramipril:** Children—1.5 mg/m²/24 hour (O) once daily, adolescents—2.5 mg/OD.
- **Ranitidine (Ranitine):** 1 to 4 mg/kg/day (O, IM, IV) in 2 to 3 divided doses.
- **Reserpine (Serpasil):** 0.07 mg/kg/dose (IM) every 8–24 hours for acute hypertension as in acute nephritis; 0.02 mg/kg/day (O) in 3 to 4 divided doses for chronic hypertension.
- **Ribavirin (Tribavirin):** Continuous aerosolization for 12 to 18 hours daily for 3 to 7 days.
- **Rifampicin (Rifamycin):** 10 to 20 mg/kg/day (O) in single daily dose.
- **Riboflavin:** Oral 50 mg once daily.
- **Roxithromycin (Rulide, Ralrox, Roxid, Rokcid, Zerox):** 5 mg/kg/day in 2 divided doses.
- **Risperidone:** 0.5–2 mg (O) once daily in aggressive behavior/Tourette syndrome.
- **Salbutamol (Salbetol, Brethmol):** 0.2 to 0.4 mg/kg/day in 3 divided doses.
- **Salmeterol:** 1 to 2 puffs (21 µg) aerosol 12 hourly. Titrate to desired effect.
- **Secnidazole (Secnil):** 30 mg/kg with a maximum of 2 g as a single dose once only.
- **Sisomicin sulfate (Ensamycin):** Under 2 weeks—5 mg/kg/day in 3 divided doses; 4 weeks—6 mg/kg/day in 3 divided doses; 4 weeks to 1 year—4.5 to 6 mg/kg/day in 3 divided doses; above 1 year—3 to 4.5 mg/kg/day in 3 divided doses.
- **Silymarin:** 70–140 mg 2–3 times daily.
- **Sodium bicarbonate:** Roughly 1–2 mEq/kg/dose. Also See Chapter 16 (Fluids, Electrolytes and Acid-base Balance and its Disturbances).
- **Sodium valproate:** 20 to 30 mg/kg (under 20 kg), 50 mg/kg (over 20 kg) in 2 to 3 divided doses. Start with relatively smaller dose (say 10 mg/kg/day) and increase by increments of 5 to 10 mg at 3 to 7 days intervals to the maximum dose.
- **Spironolactone (Aldactone):** 1.5 to 3 mg/kg/day (O).
- **Spiramycin:** In pregnant females/or confirmed toxoplasmosis infection—1.5 g (4.5 IU) until term.
- **Streptomycin Sulfate:** 20 to 50 mg/kg/day (IM), 1 to 2 mg/kg/day (IT), 100 mg/kg/day (O) in divided doses.
- **Stilbestrol:** Oral 1 mg twice a day for 2 days before test.
- **Streptokinase:** IV infusion over 30 minutes 2000 units/kg, 2.5 lakhs units followed by continuous infusion of 5000–2000 units/kg/hour.
- **Sucralfate:** Oral less than 2 years—250 mg, 1–12 years 895 500 mg, 12–18 years 1 g 4–6 times daily.
- **Sulfadiazine:** 100–150 mg/kg/day (O); 100 mg/kg/day (IV) in 4 divided doses.
- **Sulfamethoxypyrazine-pyrimethamine (SMP) (Metakelfin when combined with pyrimethamine):** 25 mg/kg as a single dose.
- **Sulfasalazine:** 40 to 75 mg/kg/day in 3 to 4 divided doses, not to exceed 6 g/day. Maintenance dose 30 to 50 mg/kg/day in 3 to 4 divided doses.
- **Sulfisoxazole (Gantrisin):** 75 to 150 mg/kg/day (O), 50 to 100 mg/kg/day (IV) in 4 to 6 divided doses.
- **Surfactant:** 4 mL/kg/dose (IT); 4 aliquots are administered intratracheally in varying positions.
- **Terbutaline sulfate (Bricanyl, Bronkine):** 0.2 mg/kg/day (O), 0.005 mg/kg/dose (SC); IV infusion may be given in difficult cases of bronchial asthma.
- **Terfenadine (Terfid):** 2 to 4 mg/kg/day in 2 divided doses, 3 to 6 years 30 mg/day in 2 divided doses, 6–12 years 60 mg/kg/day in 2 divided doses, adolescents 120 mg/day in 2 divided doses.
- **Tetanus immunoglobulin:** Treatment of tetanus in children, 500 to 3000 units (IM/IV).
- **Tetrachlorethylene:** 0.1 mL/kg (O) with a maximum of 3 to 4 mL as a single dose to be given after overnight fast.
- **Tetracyclines:**
 - **Oxytetracycline (Terramycin), tetracycline hydrochloride (Achromycin) and Chlortetracycline (Aureomycin):** 25 to 50 mg/kg/day (O) in 4 divided doses; 10 to 25 mg/kg/day (IM) and 10–15 mg/kg/day (IV) in 2 divided doses.
 - **Demethylchlortetracycline (Ledermycin):** 10 mg/kg/day in 3 to 4 divided doses.
 - **Rolitetracycline (Reverin):** 15 to 20 mg/kg/day (IM, IV) in single or two divided dose.
- **Theophylline:** See aminophylline.
- **Thiacetazone:** 3 to 5 mg/kg/day (O).
- **Thyroid (Desiccated):** Infants 15 mg/day (O), children 30 mg/day (O). Increase by increments of 15 mg every 1 to 3 weeks to 60 to 180 mg single daily dose.
- **Thyroxine (Eltroxin):** Start with 50–100 mcg. Increase every 3 to 4 week by increments of 25–50 mcg to about 200–300 mcg.
- **Ticarcillin disodium (Ticar):** 75 mg/kg/dose (IV, IM).
- **Tinidazole (Tridazole, Tiniba, Probit):** 60 mg/kg/day for 3 days for intestinal amebiasis; 50 mg/kg as a single dose once only for giardiasis.
- **Tobramycin sulfate (Nebcin):** Under 7 days—4 mg/kg/day in 2 doses. Above 7 days—6 mg/kg/day in 3 doses.
- **Tranexamic acid:** 25 mg/kg/dose (O) 3 times daily. Menorrhagia—1–1.5 g/dose 3–4 times daily upto 5 days.
- **Trimeprazine tartrate (Vallergan):** 2.5–5 mg 3–4 times daily for urticaria and pruritus; 2–4 mg/kg (O) or 0.6–0.9 mg/kg (IM) 1 to 2 hours before surgery as preanesthetic medication.

- 896 ■ **Trimethadione (Tridione):** 15–50 mg/kg/day in 2–3 divided doses.
- **Trimethoprim with sulfamethoxazole (Septran, Bactrim):** 4 to 10 mg/kg/day (O) with reference to trimethoprim.
- **Urokinase:** Thromboembolic disease—loading 4400 IU/kg in 15 mL solution over 10 minutes followed by IV infusion 4400 IU/kg/hour—6–12 hours.
- **Valproic acid:** See sodium valproate.
- **Vancomycin Hydrochloride (Vancocin):** Children 45 to 60 mg/kg/day (IV infusion) in 2–3 divided doses; adolescents 0.5 g/6 hourly or 1 g every 12 hourly; neonates 15–45 mg/kg/day in divided doses, the lower dose being for low birth weight <1200 g or <7 days. Children with enlarged ventricles need higher doses.
- **Vasopressin (Pitressin):** Diabetes insipidus; 5–20 units (SC, IM) every 4 hourly. Esophageal variceal bleed; 20 units (IV) over 15 minutes.
- **Versenate Edetate calcium disodium (EDTA):** 12.5 mg/kg (IM).
- **Vigabatrin:** <12 years 15–20 mg/kg/dose, >12 years 1g/dose-maintenance—30–40 mg/kg/dose.
- **Varicella zoster IgG:** IM 0–5 years—250 (1 vial), 6–10 years—500 (2 vials), 11–14 years—3 vials, >15 years—4 vials.
- **Vinblastine:** 0.1 to 0.2 mg/kg/week (IV).
- **Vincristine:** 0.05 to 0.15 mg/kg/week (IV).
- **Vitamin C:** See ascorbic acid.
- **Vitamin D (Arachitol, Calcirol):** A massive dose of 3 (<1 year) or 6 lakh (>1 year) units (IM), to be repeated after 3–4 weeks if indicated, or 60,000 units (O)/day for 10 days.
- **Xantinol Nicotinate (Complamina, Xanthomina):** 150 to 600 mg twice daily after meals. Inj. 300–900 mg (IM, IV infusion).
- **Xylocaine Hydrochloride:** 1 mL/kg/dose (IV).
- **Xylometazoline Hydrochloride (Otrivin):** 1 to 2 drops of 0.05% solution into each nostril once or twice daily.
- **Zinc (Zincolak, Zinfate):** 0.3 mg/kg/day (O) in divided doses.
- **Zidovudine (Retrovir, Zidovir):** 12 to 22 mg/kg/day in 4 divided doses (IV) or 12 mg/kg/day in 4 divided doses (IV) or continuous IV infusion.
- **Zinc (Zn 20):** Acrodermatitis enteropathica—0.5–1 mg/kg/dose; Wilson disease—2–12 years 25–37.5 mg/dose; diarrhea—1 <6 months–10 mg elemental zinc, >6 months 20 mg elemental zinc for 2 weeks.
- **Zopiclone:** 12–18 years 3.75 mg (O) once daily at bed time.
- **Zonisamide:** 4–8 mg/kg/day twice daily.

Multiple Choice Questions

- Correct dose of acetaminophen as an antipyretic is:
 - 5 mg/kg/dose
 - 10 mg/kg/dose
 - 15 mg/kg/dose
 - 20 mg/kg/dose
 - 25 mg/kg/dose
- Spot the wrong entry in lieu of albendazole dose in a boy aged 5 years in case of intestinal parasitosis:
 - Ascariasis: 400 mg single dose
 - Symptomatic giardiasis: 400 mg daily for 5 days
 - Strongyloidiasis: 400 mg daily for 3 days
 - Tapeworms: 400 mg daily for 28 days
 - Oxyuriasis: 400 mg single dose
- Dose of cefixime is 8 mg/kg/day in 2 divided doses. In which situation will you give double the routine dose?
 - Acute tonsillitis
 - Enteric fever
 - Bacterial dysentery
 - Balantitis
 - Acute sinusitis
- Spot the 2 wrong entries in lieu of drug dose:
 - Pantaprozole: 0.4–0.8 mg/kg/dose
 - Haloperidol in rheumatic chorea: 0.2 mg/kg/day
 - Ceftibuten: 9 mg/kg once a day
 - Carbamazepine: 30–40 mg/kg/day
 - Acetazolamide in CCF: 5 mg/kg/day

contd...

5. Pick up the relatively new drug that is effective in enteric fever but in double the routine dose:

- A. Chloramphenicol
- B. Ampicillin
- C. Amoxycillin
- D. Azithromycin
- E. Ceftriaxone

Answers

1. C 2. D 3. B 4. B, D 5. D

FURTHER READING

JOURNAL ARTICLES/BOOK CHAPTERS

1. Wilson E. Drugs in children: Changing trends. *Eur Bul Pharmacother* 2015;4:342–346.
2. Wilson E, Farooq A. Tropical pharmacotherapy: A view point. *Eur Bui Pharmacother* 2013;2:132–135.

BOOK/MONOGRAPH

1. Gupte S, Gupte N. *Pediatric Drug Directory*, 8th edn. New Delhi: Jaypee 2014.

APPENDICES

APPENDIX A USEFUL NORMAL LABORATORY VALUES

Blood

Bleeding time (BT) 1 to 3 minutes
Clotting (coagulation) time (CT) 3 to 10 minutes
Erythrocyte sedimentation rate (ESR) 15 mm in first hour
Hemoglobin birth: 16 to 18 g/dL, 2 weeks: 15 to 16 g/dL, 6 months and after: 12 g/dL, later childhood and adults: 14 to 16 g/dL.
Reticulocyte count birth: 3 to 7%, later: 1 to 2% or below
Eosinophil count 2 or 3%
Platelet count above 2,00,000/cmm
Prothrombin time 10 to 15 seconds
Vitamin B₁₂ above 200 ng/dL
Bilirubin birth and neonatal period: 1 mg% or slightly more, later: 0.2 to 0.8 mg%
Conjugated bilirubin: 0 to 0.3 mg%
Cholesterol newborn: 50 to 100 mg%, infant: 70–125 mg%, 1–5 years: 100 to 200 mg%, later: 150 to 250 mg%
Glucose 60 to 100 mg%
Alkaline phosphatase 3–13 Bodansky units, 10–20 King-Armstrong units
Acid phosphatase 1 to 5 King-Armstrong units
Serum glutamic oxaloacetic transaminase (SGOT) 4–40 units
Serum glutamic pyruvate transaminase (SGPT) 5–45 units
Iron 0.04 to 0.18 mg%
Iron binding capacity 0.187 to 0.65 mg%
Proteins total: Newborn: 4.5–7.7, 1 year: 5.6–7.3, later 6.4–7.5 g/dL
Albumin: Newborn: 2.5–5.0, 1 year: 3.5–5.0, later 3.7–5.0 g/dL.

Urine

Pus cells newborn: 0–5, infant: 2–4, later: 2–4 or less/high power field on a centrifuged sample.
Red cells newborn: 0 to 1, later: nil/high power field on a centrifuged sample.
Proteins newborn: traces, later: nil
Casts: Nil

Cerebrospinal Fluid (CSF)

Pressure 70 to 200 mm of water
Glucose 50–75 mg% (usually 20 mg% less than blood glucose level); between 6 months to 10 years, CSF sugar may normally be 70–90 mg%.
Proteins 20 to 50 mg% (80% is the albumin component); ventricular and cisternal fluids contain far less proteins than in lumbar fluid.
Chlorides 110–130 mEq/L (higher range is for grown-up children).
Cell count below 1 year: 0–10, 1–4 years: 0–8, 5 years and later: 0–5 cells/cmm.

APPENDIX B IMPORTANT CONVERSIONS

Milliequivalents

Milliequivalents (mEq) per liter = $\frac{\text{milligrams percent} + 10}{\text{atomic weight}} \times \text{valency}$

With this formula, the number of reacting particles in a liter of solution can be determined by dividing the atomic weight of each

ion into the total quantity (in milligrams) of that particular ion in one liter of solution. The resulting figure multiplied by the valency of the ion of this basis.

Data for Conversion of Milligrams per 100 mL to Milliequivalents per Liter of Plasma

Sodium (Na) = $\frac{\text{mg per 100 ml} \times 10}{23 (\text{atomic weight})} \times 1 (\text{valency}) = \text{mEq per liter}$

Potassium (K) = $\frac{\text{mg per 100 ml} \times 10}{39} \times 1 (\text{valency}) = \text{mEq per liter}$

Calcium (Ca) = $\frac{\text{mg per 100 ml} \times 10}{40} \times 2 (\text{valency}) = \text{mEq per liter}$

Chloride (Cl) = $\frac{\text{mg per 100 ml} \times 10}{35.5} \times 1 (\text{valency}) = \text{mEq per liter}$

Factors for Rapid Conversion of Milligrams per 100 mL to Milliequivalents per Liter

Cations	Factors	Anions	Factors
Sodium (Na)	0.435	Bicarbonate (HCO ₃)	0.455
Potassium (K)	0.257	Chloride (Cl)	0.286
Calcium (Ca)	0.5	Chloride (as NaCl)	0.150
Magnesium (Mg)	0.833	Phosphate (HPO ₄)	0.58
		Sulphate (SO ₄)	0.625

Temperature

Conversion of °C to °F = $(9/3X^{\circ}\text{C}) + 32 = ^{\circ}\text{F}$

Conversion of °F to °C = $5/9 (^{\circ}\text{F} - 32) = ^{\circ}\text{C}$

Inches to Centimeter

1 inch = 2.54 cm

1 cm = 0.39 inch

Minim to Millilit (mL)

1 minim = 0.06 mL

1 mL = 15 minims

Equivalent Imperial and Metric Quantities

1 grain = 65 milligrams

1 ounce = 28 grams

1 pound = 453 g

2.2 pounds = 1 kg

Centigrade to fahrenheit temperature reading							
°C	°F	°C	°F	°C	°F	°C	°F
0	= 32	35.5	= 95.9	40	= 104	60	= 140
5	= 41	36	= 96.8	40.5	= 104.9	65	= 149
10	= 50	36.5	= 97.7	41	= 105.8	70	= 158
15	= 59	37	= 98.6	41.5	= 106.7	75	= 167
20	= 68	37.5	= 99.5	42	= 107.6	80	= 176
25	= 77	38	= 100.4	43	= 109.4	85	= 185
30	= 86	38.5	= 101.3	45	= 113	90	= 194
32	= 89.6	39	= 102.2	50	= 122	95	= 203
35	= 95	39.5	= 103.2	55	= 131	100	= 212

Pounds to Kilograms 1 kg = 2.2 lb; 1 lb = 0.4536 kg

lb	kg	lb	kg	lb	kg	lb	kg
5	2.3	60	27.2	115	52.2	170	77.1
10	4.5	65	29.5	120	54.4	175	79.4
15	6.8	70	31.7	125	56.7	180	81.6
20	9.1	75	34.0	130	58.9	185	83.9
25	11.3	80	36.3	135	61.2	190	86.2
30	13.6	85	38.6	140	63.5	195	88.5
35	15.9	90	40.8	145	65.8	200	90.7
40	18.1	95	43.1	150	68.0	205	93.0
45	20.4	100	45.4	155	70.3	210	95.3
50	22.7	105	47.6	160	72.6	215	97.5
55	25.0	110	49.9	165	74.8	220	98.8

Feet and inches to centimeters

ft	in	cm	ft	in	cm	ft	in	cm	ft	in	cm
0	6	15.2	2	7	78.7		10	116.8	5	1	159.4
1	0	30.5	5	8	81.2		11	119.3	5	2	157.5
1	6	45.7	2	9	83.8		0	121.9	5	3	160.0
1	7	48.3	2	10	86.3		1	124.4	5	4	162.6
1	8	50.8	2	11	88.8		2	127.0	5	5	165.1
1	9	53.3	3	0	91.4	4	3	129.5	5	6	167.6
1	10	55.9	3	1	93.9	4	4	132.0	5	7	170.2
1	11	58.9	3	1	96.4	4	5	134.6	5	8	172.7
2	0	61.0	3	3	99.0	4	6	137.1	5	9	175.3
2	1	63.5	3	4	101.6	4	7	139.6	5	10	177.8
2	2	66.0	3	5	104.1	4	8	142.2	5	11	180.3
2	3	68.6	3	6	106.6	4	9	144.7	6	0	182.9
2	4	71.1	3	7	109.2	4	10	147.3	6	1	185.4
2	5	73.6	3	8	111.7	4	11	149.8	6	2	188.0
2	6	76.1	3	9	114.2	5	0	152.4	6	3	190.5

Conversion Factors for SI Units

	Molecular weight (MW)	From SI units	To SI units
Amino acid nitrogen	14.01		
• Plasma		mmol/l × 1.40 = mg/dL	mg/dL × 0.714 = mmol/l
• Urine		mmol/24 hr × 14.01 = mg/24 hr	mg/24 hr × 0.0714 = mmol/24 hr
Ammonium	17.03	μmol/l × 1.703 = μdL	μg/dL × 0.587 = μmol/l
Barbiturate	184.2	μmol/l × 0.0184 = mg/dL	mg/dL × 54.20 = μmol/l
Bilirubin	584.7	μmol/l × 0.015 = mg/dL	mg/dL × 17.1 = μmol/l
Calcium	40.08		
• Plasma		mmol/l × 4.008 = mL/dL	mg/dL × 0.250 = mmol/l
• Urine		mmol/24 hr × 40.08 = mg/24 hr	mg/24 hr × 0.0250 = mmol/24 hr
Catecholamines (Urine)	183.2	μmol/24 hr × 183 = μg/24 hr	μg/24 hr × 0.00546 = μmol/24 hr
Cholesterol	386.7	mmol/l × 31.7 = mg/dL	mg/dL × 0.0359 = mmol/l
Copper	63.54		
• Plasma		μmol/l × 6.35 = μg/dL	μg/dL × 0.157 = μmol/l
• Urine		μmol/24 hr × 63.5 = μg/24 hr	μg/24 hr × 0.0157 = μmol/24 hr
Cortisol	362.5	nmol/l × 0.0362 = μg/dL	μg/dL × 27.6 = nmol/24 hr
Creatinine	113.1		
• Plasma		μmol/l × 0.0113 = mg/dL	mg/dL × 88.4 = μmol/l
• Urine		mmol/24 hr × 0.113 = g/24 hr	g/24 hr × 88.4 = mmol/24 hr

SI Unit Conversion

The SI system (System International d' Units) is an international system of units now generally employed in the basic sciences, and it has now been adopted in clinical biochemistry in the United Kingdom and many other countries. It has replaced the somewhat empirical range of units (e.g. mg/100 mL, mEq/l) with which clinicians have long been familiar but which has often varied from one laboratory to another. While international standardization is obviously desirable, the change to the SI unitage will involve clinicians in the task of assimilating quite a new range of normal values with the obvious dangers of misinterpretation of laboratory reports while they adjust to a new and unfamiliar system. In order to avoid such confusion, the following short account of SI unit conversion may be in order.

The new unit for chemical measurement of quantity, where the molecular weight (MW) of the substance being measured is known and expressed in grams, is the mole.

$$\text{Number of moles (mol)} = \frac{\text{wt in g}}{\text{MW}}$$

The more common decimal fractions will be millimoles (mmol:10⁻³), micromoles (μmol:10⁻⁶), nanomoles (nmol:10⁻⁹) and picomoles (pmol:10⁻¹²). Although this SI unit of volume is the cubic metre (m³), the liter is accepted as exactly equivalent to one cubic decimeter (dm³) and in clinical biochemistry is the unit of volume. The units of concentration will, therefore, be mmol/l, μmol/l and nmol/l. However, where the molecular weight of the substance being measured is unknown or uncertain the units will be in grams or milligrams per liter, e.g. a total serum protein of 70 g/100 mL becomes 60 g/l.

Example

Results previously expressed as mEq/L

$$\begin{aligned} \text{Number of equivalents} &= \frac{\text{wt in g}}{\text{equivalent wt}} \\ &= \frac{\text{wt in g} \times \text{valency}}{\text{MW}} \end{aligned}$$

In the case of univalent ions such as Na and K, and units will remain the same. A serum Na of 140 mEq/L becomes 140 mmol/l. For polyvalent ions the old units are divided by the valency. For instance, a serum Ca of 5 mEq/L becomes 2.5 mmol/l.

contd...

	Molecular weight (MW)	From SI units	To SI units
Ethanol (alcohol)	46.07	$\text{mmol/l} \times 4.607 = \text{mg/dL}$	$\text{mg/dL} \times 0.0217 = \text{mmol/l}$
Fat (fecal)	284.5	$\text{mmol/24 hr} \times 0.284 = \text{g/24 hr}$	$\text{g/24 hr} \times 3.52 = \text{mmol/24 hr}$
Fibrinogen	Uncertain	$\text{g/l} \times 100 = \text{mg/dL}$	$\text{mg/dL} \times 0.01 = \text{g/l}$
Glucose	180.2		
• Blood or plasma		$\text{mmol/l} \times 18.02 = \text{mg/dL}$	$\text{mg/dL} \times 0.0555 = \text{mmol/l}$
• Urine		$\text{mmol/l} \times 0.0180 = \text{mg/dL}$	$\text{g/dL} \times 55.5 = \text{mmol/l}$
• CSF		as for blood or plasma	as for blood or plasma
HMMA or VMA (urine)	198.2	$\mu\text{mol/24 hr} \times 0.198 = \text{mg/24 hr}$	$\text{mg/24 hr} \times 5.05 = \mu\text{mol/24 hr}$
Hydroxyproline (urine)	131.1	$\text{mmol/24 hr} \times 131.1 = \text{mg/24 hr}$	$\text{mg/24} \times 0.00763 = \text{mmol/24 hr}$
Iron and TIBC	55.85	$\mu\text{mol/l} \times 5.59 = \mu\text{g/dL}$	$\mu\text{g/dL} \times 0.179 = \mu\text{mol/l}$
Lead	207.2		
• Blood		$\mu\text{mol/L} \times 20.7 = \mu\text{g/dL}$	$\mu\text{g/dL} \times 0.0483 = \mu\text{mol/l}$
• Urine		$\mu\text{mol/24 hr} \times 207 = \mu\text{g/24 hr}$	$\mu\text{g/24 hr} \times 0.00483 = \mu\text{mol/24 hr}$
Magnesium	24.31		
• Plasma		$\text{mmol/l} \times 2.43 = \text{mg/dL}$	$\text{mg/dL} \times 0.411 = \text{mmol/l}$
• Urine		$\text{mmol/24 hr} \times 24.3 = \text{mg/24 hr}$	$\text{mg/24 hr} \times 0.0411 = \text{mmol/29 hr}$
Estriol (urine)	288.4	$\mu\text{mol/24 hr} \times 0.228 = \text{mg/24 hr}$	$\text{mg/24 hr} \times 3.47 = \mu\text{mol/24 hr}$
17-Oxosteroids (urine)	288.4	$\mu\text{mol/24 hr} \times 0.288 = \text{mg/24 hr}$	$\text{mg/hr} \times 3.47 = \mu\text{mol/24 hr}$
Phenylalanine	165.2	$\mu\text{mol/l} \times 0.0165 = \text{mg/dL}$	$\text{mg/dL} \times 60.5 = \mu\text{mol/l}$
Phosphate	30.97		
• Serum		$\text{mmol/l} \times 3.10 = \text{mg/dL}$	$\text{mg/dL} \times 0.323 = \text{mmol/l}$
• Urine		$\text{mmol/24 hr} \times 0.0310 = \text{g/24 hr}$	$\text{g/24 hr} \times 32.3 = \text{mmol/24 hr}$
Preganediol (urine)	320.5	$\text{mmol/24 hr} \times 0.320 = \text{mg/24 hr}$	$\text{mg/24 hr} \times 3.12 = \mu\text{mol/24 hr}$
Pregnanetriol (urine)	336.5	$\text{mmol/24 hr} \times 0.336 = \text{mg/24 hr}$	$\text{mg/24 hr} \times 2.97 = \mu\text{mol/24 hr}$
Protein	Uncertain	$\text{g/l} \times 0.1 = \text{g/dL}$	$\text{g/dL} \times 10 = \text{g/l}$
Serum albumin	Uncertain	$\text{g/l} \times 0.1 = \text{g/dL}$	$\text{g/dL} \times 10 = \text{g/l}$
CSF protein	Uncertain	$\text{g/l} \times 100 = \text{mg/dL}$	$\text{mg/dL} \times 0.01 = \text{g/l}$
Protein-bound iodine	126.9	$\text{nmol/l} \times 0.0127 = \mu\text{g/dL}$	$\text{mg/dL} \times 78.8 = \text{mmol/l}$
Salicylate	138.1	$\text{mmol/l} \times 13.81 = \text{mg/dL}$	$\text{mg/dL} \times 0.0724 = 0.0724 = \text{mmol/l}$
Thyroxine	776.9	$\text{nmol/l} \times 0.0777 = \mu\text{g/dL}$	$\text{ng/dL} \times 12.87 = \text{nmol/l}$
Triiodothyronine	651.01	$\text{nmol/l} \times 0.651 = \text{ng/dL}$	$\text{ng/dL} \times 1.54 = \text{nmol/l}$
Triglyceride	885.4	$\text{mmol/l} \times 88.5 = \text{mg/dL}$	$\text{mg/dL} \times 0.0113 = \text{mmol/l}$
Urate ($\mu\text{ric acid}$)	168.1	$\text{mmol/l} \times 16.81 = \text{mg/dL}$	$\text{mg/dL} \times 0.0596 = \text{mmol/l}$
Urea	60.06	$\text{mmol/l} \times 6.01 = \text{mg/dL}$	$\text{mg/dL} \times 0.166 = \text{mmol/l}$
PO ₂	–	$\text{kPa} \times 7.52 = \text{mmHg}$	$\text{mmHg} \times 0.133 = \text{kPa}$
PCO ₂	–		
Units of energy	–	$\text{Joules (kJ)} \times 0.238 = \text{calories}$	$\text{calories} \times 4.2 = \text{Joules (kJ)}$

Abbreviations: CSF, cerebrospinal fluid; VMA, vanillyl mandelic acid; TIBC, total iron binding capacity.

Results Previously Expressed as mg/100 mL

The method of conversion to mmol/l is to divide by the molecular weight (to convert from mg to mmol) and to multiply by 10 (to convert from 100 mL to a liter). For example, the molecular weight of urea is 60 and of glucose 180 but concentrations of urea of 60 mg/100 mL and of glucose of 180 mg/100 mL both become 10 mmol/l.

The SI unit of pressure is the pascal (Pa) and in the range at present usually expressed as mm of mercury the appropriate unit is the kilo-pascal (kPa). This unit, however, may not be brought into clinical use for some time.

For some of the more important measurements a ready means of interconversion of the SI unit and the obsolescent unit in two forms, (1) conversion multiplication factors, (2) nomograms is available. It should be noted that the expression “100 mL” should now be shown

as “deciliter (dL)”. Certain substances, such as enzyme activities, will continue to be expressed in units of various types and cannot be expressed in SI units.

APPENDIX C INTERNATIONAL DAYS

7th March	Measles Immunization Day
8th March	International Women's Day
15th March	World Handicapped Day
20th March	International Day of Happiness
21st March	World Forest Day
7th April	World Health Day
18th April	World Heritage Day
22nd April	Earth Day

902	30th April	Child Labor Day
	3rd May	World Asthma Day
	15th May	International Family Day
	22nd May	International Day for Biological Diversity
	31st May	World No Tobacco Day
	5th June	World Environment Day
	21st June	International Day of Yoga
	26th June	Anti Drug Abuse Day
	1st July	Doctors Day
	11th July	World Population Day
	29th July	World ORS Day
	1st–7th August	Breastfeeding Week
	12th August	International Youth Day
	8th September	World Literacy Day
	21st September	International Day of Peace
	27th September	World Tourism Day
	1st October	Blood Donation Day
	3rd October	World Nature Day
	4th October	World Animal Welfare Day
	5th October	World Heart Day
	8th October	World Senior Citizens Day
	11th October	International Day of the Girl Child
	16th October	World Food Day
	21st October	Global Iodine Deficiency Disorder
	24th October	United Nations Day
	10th November	World Immunization Day
	1st December	World AIDS Day
	10th December	Human Rights Day
	23rd December	Farmers Day

APPENDIX D WORLD HEALTH DAY (APRIL 7) THEMES

1950	Know your own health services
1951	Health for your child and world's children
1952	Healthy surrounding make healthy people
1953	Health is wealth
1954	The nurse, pioneer of health
1955	Clean water means better health
1956	Destroy disease carrying insects
1957	Food and health
1958	Ten years of health progress
1959	Mental illness and mental health in world today
1960	Malaria eradication, a world challenge
1961	Accidents need not happen
1962	Preserve sight, prevent blindness
1963	Hunger-Disease of millions
1964	No truce for tuberculosis
1965	Smallpox constant alert
1966	Man and his cities
1967	Partners in health
1968	Health in the world of tomorrow
1969	Health, labor and productivity
1970	Early detection of cancer saves lives
1971	A full life despite disabilities
1972	Your heart is your health
1973	Health begins at home
1974	Better food for healthier world
1975	Smallpox: Point of no return
1976	Foresight prevents blindness
1977	Immunize and protect your child
1978	Down with high blood pressure
1979	A healthy child a sure future
1980	Smoking or health, the choice is yours
1981	Health for all by the year 2000 AD
1982	Add life to years

1983	Health for all by 2000 AD: Count down has begun
1984	Children's health tomorrow's wealth
1985	Healthy youth our best resource
1986	Healthy living: Everyone a winner
1987	Immunization: A chance for every child
1988	Health for all, all for health
1989	Let us talk health
1990	Our planet, our health: Think globally, act locally
1991	Disaster: Are we prepared?
1992	Heart beat: The rhythm of health
1993	Handle life with care: Prevent violence and negligence
1994	Oral health for a healthy life
1995	Target 2000: A world without polio
1996	Healthy cities for better life
1997	Emerging infectious diseases: Global alert, global response
1998	Safe motherhood: Pregnancy is special, let's make it safe
1999	Active aging makes the difference
2000	Safe blood starts with me: Blood saves lives
2001	Stop exclusion: "Dare to Care"
2002	Move for health
2003	Shape for future of life
2004	Road safety is no accident
2005	Make every mother and child count
2006	Working together for health
2007	International health security
2008	Protecting health from climate changes
2009	Save lives, make hospitals safe in emergencies
2010	Urbanization and health
2011	Antimicrobial resistance: No action today, no cure tomorrow
2012	Good health adds life to years
2013	Control your blood pressure, control your life
2014	Small bite, big threat of vector-borne diseases
2015	From farm to plate: Make food safe
2016	Scale up prevention, strengthen care and enhance surveillance

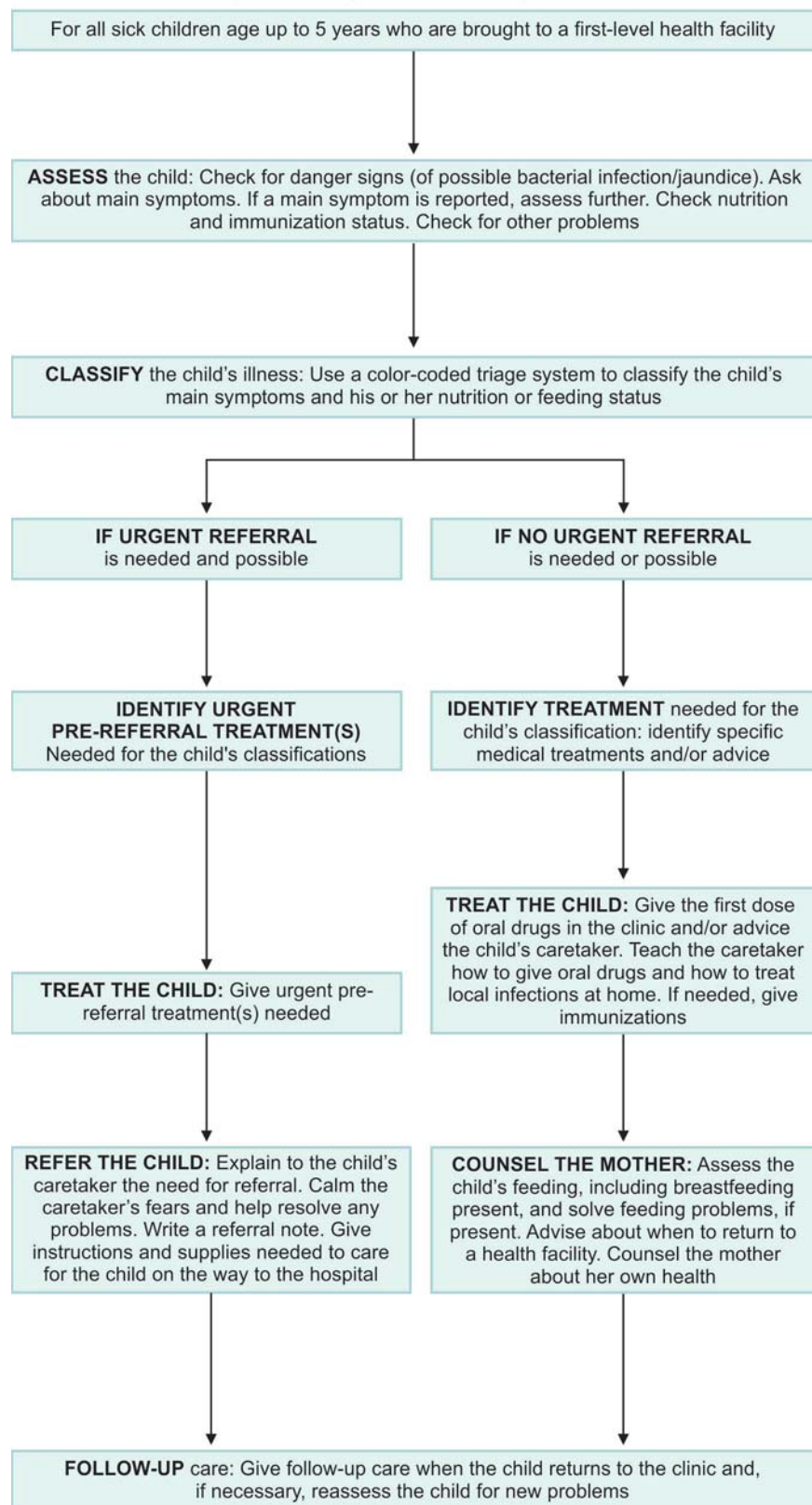
APPENDIX E WORLD BREASTFEEDING WEEK (AUGUST 1 TO 6) THEMES

1992	Baby-friendly hospitals
1993	Mother-friendly workplace
1994	Protect breastfeeding: Making the code work
1995	Breastfeeding: Empowering women
1996	Breastfeeding: A community responsibility
1997	Breastfeeding: Nature's way
1998	Breastfeeding: The best investment
1999	Breastfeeding and education
2000	Breastfeeding: It's your right
2001	Breastfeeding in the information age
2002	Healthy mothers and healthy babies
2003	Breastfeeding in a globalized world for peace and justice
2004	Exclusive breastfeeding: Safe, sound and sustainable
2005	Breastfeeding and family foods—loving and healthy
2006	The IMS act: Making it known to people
2007	Breastfeeding: The first hour—save one million babies
2008	Mother's support: Babies going for the gold
2009	Breastfeeding: A vital emergency response
2010	Breastfeeding: Just 10 steps: The baby friendly way
2011	Breastfeeding: A 3D experience
2012	Breastfeeding: Understanding the past, planning the future
2013	Breastfeeding support: Close to mothers
2014	Breastfeeding: A winning goal for life
2015	Breastfeeding and work: Let's make it work

APPENDIX F

THE IMNCI CASE MANAGEMENT PROCESS

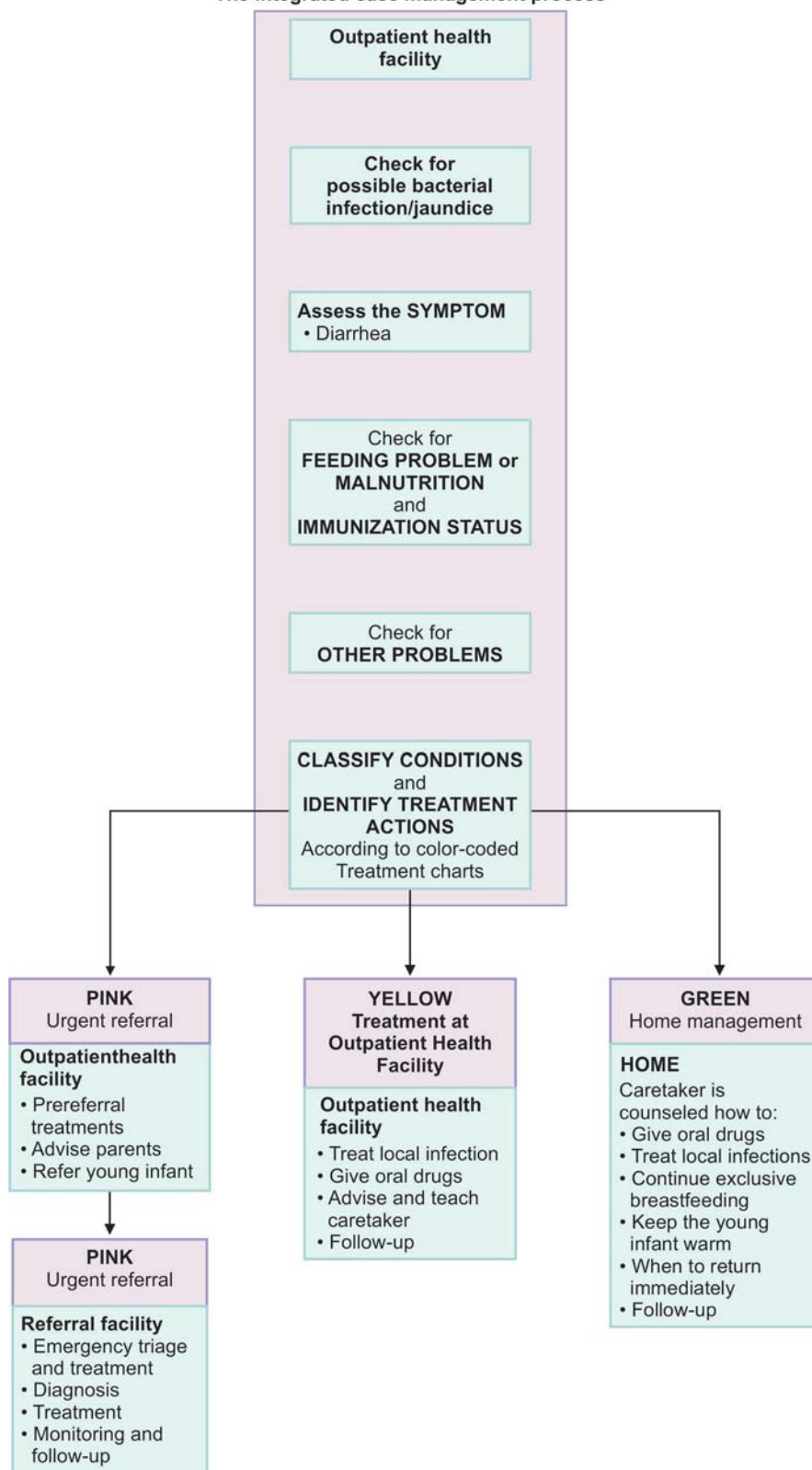
Summary of the integrated Case Management Process



APPENDIX G

IMNCI CASE MANAGEMENT IN THE OUTPATIENT HEALTH FACILITY, FIRST-LEVEL REFERRAL FACILITY AND AT HOME FOR THE SICK YOUNG INFANT UPTO 2 MONTHS AGE

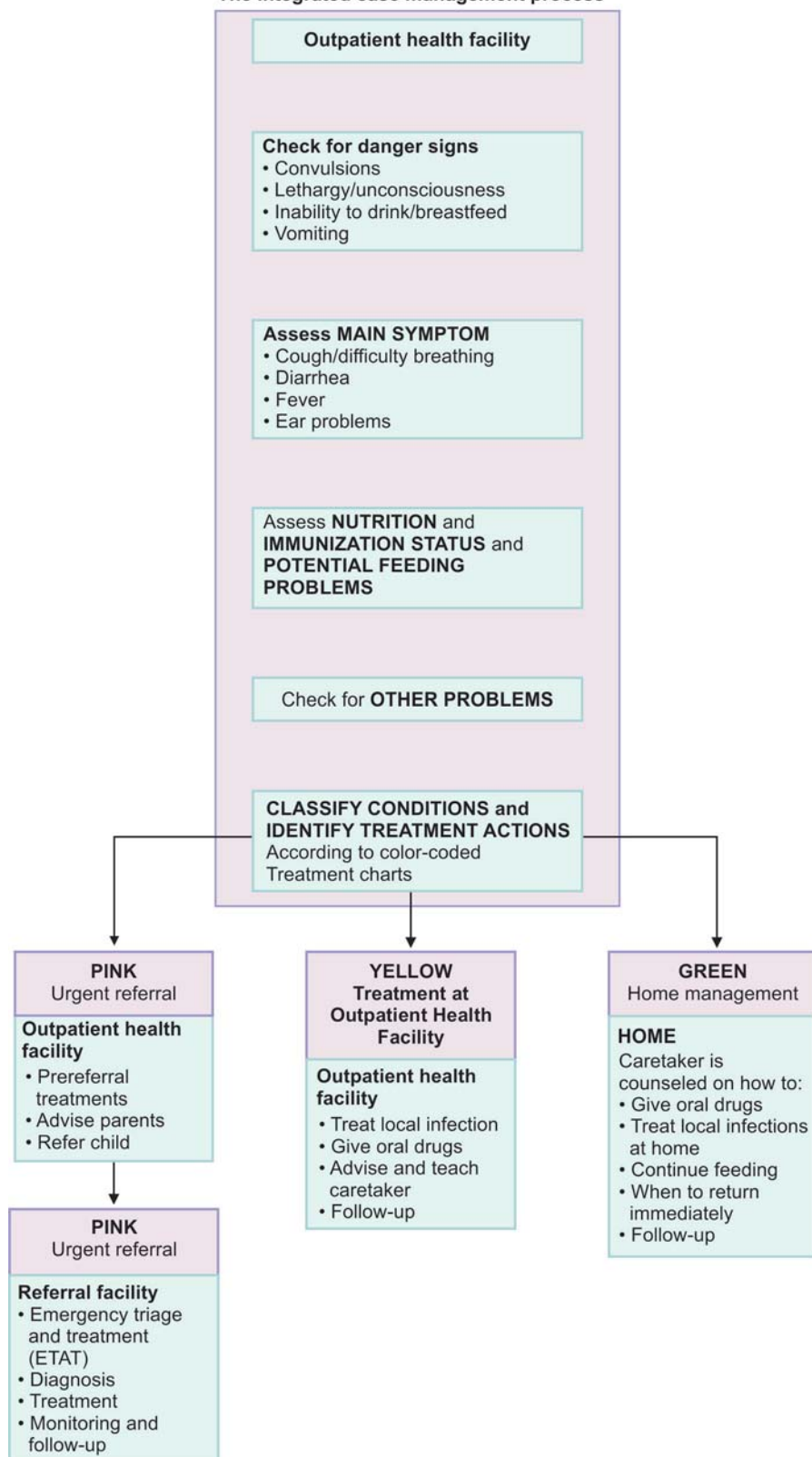
The integrated case management process



APPENDIX H

IMNCI CASE MANAGEMENT IN THE OUTPATIENT HEALTH FACILITY, FIRST-LEVEL REFERRAL FACILITY AND AT HOME FOR THE SICK CHILD FROM AGE 2 MONTHS UPTO 5 YEARS

The integrated case management process



APPENDIX I**SYLLABUS MODULE OF DIDACTIC TEACHING FOR UNDERGRADUATES AS PER RECOMMENDATION OF THE MEDICAL COUNCIL OF INDIA (MCI)**

(* Student MUST KNOW all the below listed topics except those marked with an astrisk which they SHOULD KNOW)

1. Introduction to Pediatrics

- 1.1 Importance of child health and its determinants, approach to a child patient and his/her family.
- 1.2 Age distribution of pediatric patients, anatomical and developmental factors affecting childhood illnesses.
- 1.3 Common causes of childhood morbidity and mortality and indices of child health.
- 1.4 First-aid procedures—cardiopulmonary resuscitation, shock, anaphylaxis and common poisonings.
- 1.5 National programs pertaining to child health.

2. Growth and Development

- 2.1 Definitions, determinants of growth, assessment of growth and concept of percentiles.
- 2.2 Growth and sexual development during childhood and adolescence, anthropometry, velocity of growth, growth monitoring and road-to-health card.
- 2.3 Developmental milestones, determinants of normal development and factors affecting development of children.
- 2.4 Assessment of development—gross motor, fine motor, language, social and adaptive, concept of developmental quotient.
- 2.5 Approach to a child with failure to thrive, growth retardation and short stature.

3. Nutrition and Its Disorders

- 3.1 Age-related requirements of calories, nutrients, vitamins, minerals and trace elements.
- 3.2 Infant feeding practices—breastfeeding, artificial/bottle feeding and weaning.
- 3.3 Protein-energy malnutrition—ecology, diagnosis, anthropometry, growth charts and clinical features.
- 3.4 Associated deficiencies and complications of protein-energy malnutrition and its management.
- 3.5 Deficiency disorders related to fat soluble vitamins (vitamins 'A', 'D', 'E' and 'K').
- 3.6 Deficiency disorders related to water soluble vitamins.
- 3.7 Nutritional anemias in infancy and childhood.

4. Immunizations

- 4.1 Introduction, active and passive immunizations, national immunization schedule, contraindications and adverse reactions to vaccines.
- 4.2 Universal Immunization Program (UIP), Expanded Program of Immunization (EPI), cold chain, logistics, techniques of vaccinations, etc.

5. Fluid and Electrolytes

- 5.1 Pathophysiology of fluid, electrolytes and acid-base balance and principles of management (2 lectures).

6. Neonatology

- 6.1 Definitions, health indices, classification, identification of high risk newborn baby.
- 6.2 Care of newborn baby at birth including cardiopulmonary resuscitation.
- 6.3 Care of the normal newborn baby including breastfeeding.
- 6.4 Common minor development neonatal problems.
- 6.5 Neonatal infections including superficial infections, septicemia and tetanus neonatorum.
- 6.6 Problems and management of low birth weight babies in the hospital and community.

- 6.7 Common congenital malformations and identification of life threatening surgical emergencies in the newborn.
- 6.8 Neonatal jaundice.
- 6.9 Respiratory distress in a newborn baby.*
- 6.10 Effect of maternal medications on the fetus and suckling infant.

7. Infectious Diseases (I)

- 7.1 Common childhood exanthematous illnesses: measles, rubella, chickenpox.
- 7.2 Mumps and whooping cough.
- 7.3 Typhoid fever.
- 7.4 Diphtheria.
- 7.5 Tuberculosis (2 lectures).

8. Infectious Diseases/Parasitic Disorders (II)

- 8.1 Common infections: roundworms, thread-worms, hookworms, etc.
- 8.2 Malaria including cerebral malaria and its management.
- 8.3 Amebic dysentery and giardiasis.

9. Gastrointestinal System

- 9.1 Acute diarrhea and dysentery—epidemiology, etiology, pathophysiology and clinical manifestations.
- 9.2 Acute diarrhea—assessment of dehydration, management, including oral rehydration therapy (ORT) and nutritional management.
- 9.3 Persistent diarrhea in infants.*
- 9.4 Abdominal pain in children.
- 9.5 Jaundice in a child.
- 9.6 Some common GI symptoms—vomiting, constipation, rectal bleeding.

10. Respiratory System

- 10.1 Acute upper respiratory infections including common cold, acute streptococcal pharyngitis, otitis media and croup.
- 10.2 Acute lower respiratory infections (pneumonias): epidemiology, etiology, clinical features, management, including community-based treatment and prevention.
- 10.3 Bronchial asthma.

11. Cardiovascular System

- 11.1 Congestive heart failure—causes, diagnosis and management.
- 11.2 Congenital heart disease.*
- 11.3 Rheumatic fever and rheumatic heart disease.

12. Genitourinary System

- 12.1 Acute glomerulonephritis, hematuria and related problems.
- 12.2 Nephrotic syndrome.
- 12.3 Urinary tract infections—acute and recurrent.

13. Hemato-oncology

- 13.1 Hemolytic anemias in children.*
- 13.2 Acute leukemias and lymphomas.*
- 13.3 Solid tumors in children.*

14. Central Nervous System and Neuromuscular Disorders

- 14.1 Epilepsy including febrile convulsions.
- 14.2 Pyogenic meningitis.
- 14.3 Tuberculous meningitis.
- 14.4 Cerebral palsy—etiology, classification, clinical features, management.
- 14.5 Mental retardation—etiology, clinical diagnosis and classification, preventable/treatable causes, simple laboratory screening and management.
- 14.6 Hydrocephalus and microcephaly.*
- 14.7 Myopathies.*
- 14.8 Acute poliomyelitis and its sequelae.

15. Endocrine System

- 15.1 Cretinism—causes, early diagnosis and management.*
- 15.2 Juvenile diabetes mellitus.*

APPENDIX J

FINAL MBBS PART II (PEDIATRIC) EXAMINATION

Break-up

Theory	40 marks
Clinical	30 marks
Viva (theory)	10 marks
Internal assessment	20 marks (10 each for theory and practical)
Total	100 marks

Guidelines/Classifications

- Clinical
 - 2 Cases : Long case (1 hour) 15 marks
 - Short case (15 minutes) 10 marks
 - 2 Spotters: 5 marks
- "Viva (theory) marks (10) are to be added to the theory marks".
- After addition of the respective internal assessment marks, total theory marks come to 60 and practical marks to 40.
- The examiners are expected to conduct the examination in two pairs for two batches of candidates.
- Criteria for passing the examination are 50% in aggregate with a minimum of 50% in theory and 50% in clinicals/practicals.

APPENDIX K

IMPORTANT WEBSITES ON PEDIATRICS AND ALLIED FIELDS

- **Indian Pediatrics:** www.indianpediatrics.net: This free site offers full text electronic version of the journal "Indian Pediatrics" and should be of particular interest to the pediatric postgraduates, residents and other scholars and practitioners eager to remain abreast of the pediatric scenario in India.
- **Indian Journal of Pediatrics:** www.ijppediatricsindia.org: This website hosts the electronic version of the oldest Indian journal in the field of child health. The journal is now published every month. The site provides original articles, special articles, symposia, clinical briefs, letters to the editor and abstracts.
- **Synopsis:** www.pedsynopsis.com: This free site hosts the electronic version of the periodical, "Synopsis", a current survey of world literature in pediatrics, published quarterly from Detroit, USA. Each issue offers an indepth review article and summaries of articles on topical issues published in the world pediatric and allied literature with critical comments. Also incorporated is the "Morning Report at Children's Hospital at Michigan" which usually makes a very productive reading.
- **American Academy of Child and Adolescent Psychiatry:** www.aacap.org: This website hosts summaries of AACAP practice parameters. More importantly, it provides the full text of more than 50 "Facts for Families" that are fact sheets on latest and comprehensive information concerning children, adolescents and their families. An extension of this (website www.aacap.org/journal/journal.htm) takes you to the abstracts and table of contents (not the full articles) of Journal of the American Academy of Child and Adolescent Psychiatry.
- **British Pediatric Surveillance Unit:** <http://bpsu.repch.ac.uk>: The site, sponsored by the Royal College of Pediatrics and Child Health of United Kingdom, provides important details about uncommon as well as new childhood diseases. Through the site, the newsletter is also accessible.
- **Kids Health:** www.ama-assn.org/insight/h_focus/numerous/index.htm: The American Medical Association (AMA) and the Nemours Foundation have developed "The Kids Health" which is a useful source of information on children's health, primarily addressed to the parents and caregivers, even pediatricians would find it useful from the angle of education of their clients. The section on accident prevention is particularly remarkable.

- **Clinical Notebook: Nutrition Lab Values:** <http://W3.uokhsc.edu/uguild/CN2Case/notebook.html>: This is an excellent site for lab values, formulas for energy requirements and notes on clinical nutrition course.
- **Understanding Vitamins:** <http://www.critpath.org/aric/library/altern03.htm>: Balanced and referenced articles on vitamin supplementation are available in this site, especially in context of HIV/AIDS.
- **The Crusade against Malaria:** <http://www.malariaipca.com/>: This is a valuable site for upto date information on malaria worldwide, including its types, classification, clinical presentation, diagnosis, treatment and guidelines for the travellers to the endemic areas.
- **Pediatric Interactive Dialogue:** WWW.JJPED.COM: This fine website is hosted by the Department of Pediatrics, Institute of Child Health, Grant Medical College and JJ Group of Hospitals, Mumbai, India. For participation in interactive discussion, compulsory registration is a prerequisite.
- **Parasitic Diseases:** www.dpd.cdc.gov/dpdx/: This website is hosted by the Centre for Disease Control and provides, among other information, reviews of parasitic diseases globally. Health professional may seek answers related to digital images of specimens sent by them. No fee is involved.
- **Clinical Infectious Diseases:** www.journals.uchicago.edu/CID/: This site incorporates issues from 1997 onwards of the journal. No charges are taken for access to abstracts and table of contents. However, full text is accessible to only subscribers on nominal payment.
- **Doctor Speak/Consumer Speak:** This free site is hosted by the Indian Medical Portals, Mumbai, India. The "Doctor speak" section offers a prescription guide related to over 200 drugs, daily health news from the agency, Reuters, a journal containing case reports from various specialists and a medical library on diseases. The "Consumer speak" section offers a family medical reference library and a drug index for patients, including children.
- **Learn about Health:** <http://members.rediff.com/mededu/fle.htm>: This free but useful site, targeted at teenaged girls, is hosted by Dr Tejinder Singh, Professor of Pediatrics, Christian Medical College and Hospital, Ludhiana, India. With the inclusion of adolescence in "pediatrics", it can assist the practising pediatricians in their zest to create awareness among young girls about their health, development and minor problems.
- **American Journal of Perinatology:** www.thieme.com/onGILJMAEEGDH/display/755: This very useful site is free only as far as access to the table of contents and abstracts is concerned. For access to the contents, registration is required.
- **Free Medical Journals.com:** www.freemedicaljournal.com: This highly recommended site, hosted by Amedeo.com, the company famous for the noted "Vaccine Weekly", offers free access to the full contents of over a score of important journals.
- **Reuters Health:** <http://www.reuteurshealth.com/>: This very important site, hosted by the reputed Reuters news agency, offers news stories and summaries of articles from most international pediatric and other journals as also a searchable drug database. Except for the latest news and news of last 10 days. A nominal subscription is compulsory.
- **International Center for Diarrheal Disease Research (ICDDR):** <http://www.icddr.org.sg>: This site offers information on the activities of the ICDDR, Dhaka, Bangladesh, which is reputed for excellent work on diarrheal diseases with special reference to ORS, the most spectacular medical advance of the 20th century.
- **Atlas of Gastrointestinal Endoscopy:** www.mindspring.com/~atlsouthgastro/atlas_1.html: This indeed is a very fine website for those interested in endoscopic profiles. The clarity of the graphics and the effective commentary adds to its value.
- **Emerging Infectious Diseases:** www.cdc.gov/ncidod/EID/index.htm: This free site is hosted by the Center for Disease Control and aims at combating emerging infectious diseases with special reference to emerging infections.

- 908 ■ Children with Diabetes:** www.childrenwithdiabetes.com/: This site provides useful information for children with diabetes mellitus and their families. Pediatricians can recommend it to the interested parties.
- **Action for Autism:** www.autism.india.org/: This fine site is hosted by an Indian charitable organization, action for autism that offers support and services to autistic children and those working for such children in South Asia. The site offers information about the activities of the organization as also information about various aspects of autism in India.
- **Children's Vaccine Program:** www.childrenewaccine.org/: This website is sponsored by the Microsoft giant, Bill Gate. It deals with the gigantic vaccination coverage in the developing world.
- **Internet Resources for Special Children:** www.irsc.org/: This is a very useful website for obtaining information on needs of the special children those with one or the other disability. Its prime aim is to boost public awareness in relation to disabled children.
- **Neonatology and Genetics Links from Karolinska Institute:** www.mic.ki.se/Diseases/c16.html: This excellent site hosted by the Karolinska Institute Library, Sweden, provides an exhaustive collection of links to the internet resources related to genetic disorders and neonatology.
- **Monthly Index of Medical Specialties (MIMS) India:** www.mims-India.com/: This site provides the electronic version of the MIMS India, an upto-date index of ethical preparations (concerning all medical fields, including pediatrics) available for prescription in India. It is updated every month.
- **Neonatal Medicine:** <http://www.cs.nsw.gov.au/rpa/neonatal/default1.htm>: This excellent website from the Royal Prince Alfred Hospital, Sydney, Australia, is a spotlight on various protocols in the management of neonatal problems. Over and above this, you shall find information on clinical aids, drugs, procedures and links to resources in neonatology. It is available free of charge.
- **Celiac Disease:** www.celiac.org/: Straight from the famous Celiac Disease Foundation, provides patient information on various aspects of celiac disease. Besides a newsletter, you shall find useful information on screening, support groups and recent advances concerning celiac disease.

APPENDIX L

WHO CHILD GROWTH TABLES (2006)

Table A-IV.1: Length/height and weight percentiles for girls and boys aged 0–60 months

Month	Girls						Boys					
	Length/height (cm)			Weight (kg)			Length/height (cm)			Weight (kg)		
	3rd	50th	97th	3rd	50th	97th	3rd	50th	97th	3rd	50th	97th
0	45.6	49.1	52.7	2.4	3.2	4.2	46.3	49.9	53.4	2.5	3.3	4.3
1	50.0	53.7	57.4	3.2	4.2	5.4	51.1	54.7	58.4	3.4	4.5	5.7
2	53.2	57.1	60.9	4.0	5.1	6.5	54.7	58.4	62.2	4.4	5.6	7.0
3	55.8	59.8	63.8	4.6	5.8	7.4	57.6	61.4	65.3	5.1	6.4	7.9
4	58.0	62.1	66.2	5.1	6.4	8.1	60.0	63.9	67.8	5.6	7.0	8.6
5	59.9	64.0	68.2	5.5	6.9	8.7	61.9	65.9	69.9	6.1	7.5	9.2
6	61.5	65.7	70.0	5.8	7.3	9.2	63.6	67.6	71.6	6.4	7.9	9.7
7	62.9	67.3	71.6	6.1	7.6	9.6	65.1	69.2	73.2	6.7	8.3	10.2
8	64.3	68.7	73.2	6.3	7.9	10.0	66.5	70.6	74.7	7.0	8.6	10.5
9	65.6	70.1	74.7	6.6	8.2	10.4	67.7	72.0	76.2	7.2	8.9	10.9
10	66.8	71.5	76.1	6.8	8.5	10.7	69.0	73.3	77.6	7.5	9.2	11.2
11	68.0	72.8	77.5	7.0	8.7	11.0	70.2	74.5	78.9	7.7	9.4	11.5
12	69.2	74.0	78.9	7.1	8.9	11.3	71.3	75.7	80.2	7.8	9.6	11.8
13	70.3	75.2	80.2	7.3	9.2	11.6	72.4	76.9	81.5	8.0	9.9	12.1
14	71.3	76.4	81.4	7.5	9.4	11.9	73.4	78.0	82.7	8.2	10.1	12.4
15	72.4	77.5	82.7	7.7	9.6	12.2	74.4	79.1	83.9	8.4	10.3	12.7
16	73.3	78.6	83.9	7.8	9.8	12.5	75.4	80.2	85.1	8.5	10.5	12.9
17	74.3	79.7	85.0	8.0	10.0	12.7	76.3	81.2	86.2	8.7	10.7	13.2
18	75.2	80.7	86.2	8.2	10.2	13.0	77.2	82.3	87.3	8.9	10.9	13.5
19	76.2	81.7	87.3	8.3	10.4	13.3	78.1	83.2	88.4	9.0	11.1	13.7
20	77.0	82.7	88.4	8.5	10.6	13.5	78.9	84.2	89.5	9.2	11.3	14.0
21	77.9	83.7	89.4	8.7	10.9	13.8	79.7	85.1	90.5	9.3	11.5	14.3
22	78.7	84.6	90.5	8.8	11.1	14.1	80.5	86.0	91.6	9.5	11.8	14.5
23	79.6	85.5	91.5	9.0	11.3	14.3	81.3	86.9	92.6	9.7	12.0	14.8
24	80.3	86.4	92.5	9.2	11.5	14.6	82.1	87.8	93.6	9.8	12.2	15.1
25	80.4	86.6	92.8	9.3	11.7	14.9	82.1	88.0	93.8	10.0	12.4	15.3
26	81.2	87.4	93.7	9.5	11.9	15.2	82.8	88.8	94.8	10.1	12.5	15.6

contd...

Month	Girls						Boys					
	Length/height (cm)			Weight (kg)			Length/height (cm)			Weight (kg)		
	3rd	50th	97th	3rd	50th	97th	3rd	50th	97th	3rd	50th	97th
27	81.9	88.3	94.6	9.6	12.1	15.4	83.5	89.6	95.7	10.2	12.7	15.9
28	82.6	89.1	95.6	9.8	12.3	15.7	84.2	90.4	96.6	10.4	12.9	16.1
29	83.4	89.9	96.4	10.0	12.5	16.0	84.9	91.2	97.5	10.5	13.1	16.4
30	84.0	90.7	97.3	10.1	12.7	16.2	85.5	91.9	98.3	10.7	13.3	16.6
31	84.7	91.4	98.2	10.3	12.9	16.5	86.2	92.7	99.2	10.8	13.5	16.9
32	85.4	92.2	99.0	10.4	13.1	16.8	86.8	93.4	100.0	10.9	13.7	17.1
33	86.0	92.9	99.8	10.5	13.3	17.0	87.4	94.1	100.8	11.1	13.8	17.3
34	86.7	93.6	100.6	10.7	13.5	17.3	88.0	94.8	101.5	11.2	14.0	17.6
35	87.3	94.4	101.4	10.8	13.7	17.6	88.5	95.4	102.3	11.3	14.2	17.8
36	87.9	95.1	102.2	11.0	13.9	17.8	89.1	96.1	103.1	11.4	14.3	18.0
37	88.5	95.7	103.0	11.1	14.0	18.1	89.7	96.7	103.8	11.6	14.5	18.3
38	89.1	96.4	103.7	11.2	14.2	18.4	90.2	97.4	104.5	11.7	14.7	18.5
39	89.7	97.1	104.5	11.4	14.4	18.6	90.8	98.0	105.2	11.8	14.8	18.7
40	90.3	97.7	105.2	11.5	14.6	18.9	91.3	98.6	105.9	11.9	15.0	19.0
41	90.8	98.4	106.0	11.6	14.8	19.2	91.9	99.2	106.6	12.1	15.2	19.2
42	91.4	99.0	106.7	11.8	15.0	19.5	92.4	99.9	107.3	12.2	15.3	19.4
43	92.0	99.7	107.4	11.9	15.2	19.7	92.9	100.4	108.0	12.3	15.5	19.7
44	92.5	100.3	108.1	12.0	15.3	20.0	93.4	101.0	108.6	12.4	15.7	19.9
45	93.0	100.9	108.8	12.1	15.5	20.3	93.9	101.6	109.3	12.5	15.8	20.1
46	93.6	101.5	109.5	12.3	15.7	20.6	94.4	102.2	109.9	12.7	16.0	20.4
47	94.1	102.1	110.2	12.4	15.9	20.8	94.9	102.8	110.6	12.8	16.2	20.6
48	94.6	102.7	110.8	12.5	16.1	21.1	95.4	103.3	111.2	12.9	16.3	20.9
49	95.1	103.3	111.5	12.6	16.3	21.4	95.9	103.9	111.8	13.0	16.5	21.1
50	95.7	103.9	112.1	12.8	16.4	21.7	96.4	104.4	112.5	13.1	16.7	21.3
51	96.2	104.5	112.8	12.9	16.6	22.0	96.9	105.0	113.1	13.3	16.8	21.6
52	96.7	105.0	113.4	13.0	16.8	22.2	97.4	105.6	113.7	13.4	17.0	21.8
53	97.2	105.6	114.1	13.1	17.0	22.5	97.9	106.1	114.3	13.5	17.2	22.1
54	97.6	106.2	114.7	13.2	17.2	22.8	98.4	106.7	115.0	13.6	17.3	22.3
55	98.1	106.7	115.3	13.4	17.3	23.1	98.8	107.2	115.6	13.7	17.5	22.5
56	98.6	107.3	116.0	13.5	17.5	23.3	99.3	107.8	116.2	13.8	17.7	22.8
57	99.1	107.8	116.6	13.6	17.7	23.6	99.8	108.3	116.8	13.9	17.8	23.0
58	99.6	108.4	117.2	13.7	17.9	23.9	100.3	108.9	117.4	14.1	18.0	23.3
59	100.0	108.9	117.8	13.8	18.0	24.2	100.8	109.4	118.1	14.2	18.2	23.5
60	100.5	109.4	118.4	14.0	18.2	24.4	101.2	110.0	118.7	14.3	18.3	23.8

Source: WHO (available at <http://www.who.int/childgrowth/standards/en/>).

Table A-IV.2: Height and weight percentiles for girls and boys aged 5–10 years												
Year/ Month	Girls						Boys					
	Height (cm)			Weight (kg)			Height (cm)			Weight (kg)		
	3rd	50th	97th	3rd	50th	97th	3rd	50th	97th	3rd	50th	97th
5.1	100.6	109.6	118.6	14.2	18.3	24.3	101.6	110.3	118.9	14.6	18.5	23.8
5.2	101.1	110.1	119.2	14.3	18.4	24.6	102.1	110.8	119.5	14.7	18.7	24.0
5.3	101.5	110.6	119.7	14.4	18.6	24.9	102.6	111.3	120.1	14.8	18.9	24.3
5.4	102.0	111.2	120.3	14.5	18.8	25.1	103.1	111.9	120.7	15.0	19.0	24.5
5.5	102.4	111.7	120.9	14.7	19.0	25.4	103.5	112.4	121.3	15.1	19.2	24.8

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Year/ Month	Girls						Boys					
	Height (cm)			Weight (kg)			Height (cm)			Weight (kg)		
	3rd	50th	97th	3rd	50th	97th	3rd	50th	97th	3rd	50th	97th
5.6	102.9	112.2	121.5	14.8	19.1	25.7	104.0	112.9	121.8	15.3	19.4	25.1
5.7	103.3	112.7	122.0	14.9	19.3	25.9	104.4	113.4	122.4	15.4	19.6	25.3
5.8	103.8	113.2	122.6	15.0	19.5	26.2	104.9	113.9	123.0	15.5	19.8	25.6
5.9	104.2	113.7	123.1	15.2	19.6	26.5	105.4	114.5	123.5	15.7	19.9	25.8
5.10	104.6	114.2	123.7	15.3	19.8	26.7	105.8	115.0	124.1	15.8	20.1	26.1
5.11	105.1	114.6	124.2	15.4	20.0	27.0	106.2	115.5	124.7	16.0	20.3	26.4
6.0	105.5	115.1	124.8	15.5	20.2	27.3	106.7	116.0	125.2	16.1	20.5	26.7
6.1	105.9	115.6	125.3	15.6	20.3	27.5	107.1	116.4	125.8	16.3	20.7	26.9
6.2	106.3	116.1	125.8	15.8	20.5	27.8	107.6	116.9	126.3	16.4	20.9	27.2
6.3	106.8	116.6	126.4	15.9	20.7	28.1	108.0	117.4	126.9	16.5	21.1	27.5
6.4	107.2	117.0	126.9	16.0	20.9	28.4	108.4	117.9	127.4	16.7	21.3	27.8
6.5	107.6	117.5	127.4	16.1	21.0	28.7	108.8	118.4	127.9	16.8	21.5	28.1
6.6	108.0	118.0	127.9	16.3	21.2	28.9	109.3	118.9	128.5	17.0	21.7	28.3
6.7	108.4	118.4	128.5	16.4	21.4	29.2	109.7	119.4	129.0	17.2	21.9	28.6
6.8	108.9	118.9	129.0	16.5	21.6	29.5	110.1	119.8	129.5	17.3	22.1	28.9
6.9	109.3	119.4	129.5	16.6	21.8	29.8	110.5	120.3	130.1	17.5	22.3	29.2
6.10	109.7	119.9	130.0	16.8	22.0	30.1	111.0	120.8	130.6	17.6	22.5	29.5
6.11	110.1	120.3	130.6	16.9	22.2	30.4	111.4	121.3	131.1	17.8	22.7	29.8
7.0	110.5	120.8	131.1	17.0	22.4	30.8	111.8	121.7	131.7	17.9	22.9	30.1
7.1	110.9	121.3	131.6	17.2	22.6	31.1	112.2	122.2	132.2	18.1	23.1	30.4
7.2	111.4	121.8	132.1	17.3	22.8	31.4	112.6	122.7	132.7	18.2	23.3	30.7
7.3	111.8	122.2	132.7	17.5	23.0	31.7	113.0	123.1	133.3	18.4	23.5	31.1
7.4	112.2	122.7	133.2	17.6	23.2	32.2	113.4	123.6	133.8	18.5	23.7	31.4
7.5	112.6	123.2	133.7	17.8	23.4	32.4	113.8	124.1	134.3	18.7	23.9	31.7
7.6	113.1	123.7	134.3	17.9	23.6	32.8	114.3	124.5	134.8	18.8	24.1	32.0
7.7	113.5	124.1	134.8	18.1	23.9	33.1	114.7	125.0	135.3	19.0	24.3	32.3
7.8	113.9	124.6	135.3	18.2	24.1	33.5	115.1	125.5	135.9	19.1	24.6	32.7
7.9	114.4	125.1	135.9	18.4	24.3	33.8	115.5	125.9	136.4	19.3	24.8	33.0
7.10	114.8	125.6	136.4	18.6	24.5	34.2	115.9	126.4	136.9	19.5	25.0	33.3
7.11	115.2	126.1	136.9	18.7	24.8	34.6	116.2	126.8	137.4	19.6	25.2	33.7
8.0	115.7	126.6	137.5	18.9	25.0	34.9	116.6	127.3	137.9	19.8	25.4	34.0
8.1	116.1	127.0	138.0	19.1	25.3	35.3	117.0	127.7	138.4	19.9	25.6	34.4
8.2	116.5	127.5	138.5	19.2	25.5	35.7	117.4	128.2	138.9	20.1	25.9	34.7
8.3	117.0	128.0	139.1	19.4	25.8	36.1	117.8	128.6	139.4	20.2	26.1	35.1
8.4	117.4	128.5	139.6	19.6	26.0	36.5	118.2	129.0	139.9	20.4	26.3	35.5
8.5	117.9	129.0	140.2	19.8	26.3	36.9	118.6	129.5	140.4	20.5	26.5	35.8
8.6	118.3	129.5	140.7	20.0	26.6	37.4	119.0	129.9	140.9	20.7	26.7	36.2
8.7	118.7	130.0	141.2	20.1	26.8	37.8	119.3	130.4	141.4	20.8	27.0	36.6
8.8	119.2	130.5	141.8	20.3	27.1	38.2	119.7	130.8	141.9	21.0	27.2	37.0
8.9	119.6	131.0	142.3	20.5	27.4	38.6	120.1	131.3	142.4	21.1	27.4	37.4
8.10	120.1	131.5	142.9	20.7	27.6	39.1	120.5	131.7	142.9	21.3	27.6	37.8
8.11	120.5	132.0	143.4	20.9	27.9	39.5	120.9	132.1	143.4	21.4	27.9	38.2
9.0	121.0	132.5	144.0	21.1	28.2	40.0	121.3	132.6	143.9	21.6	28.1	38.6

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Year/ Month	Girls						Boys					
	Height (cm)			Weight (kg)			Height (cm)			Weight (kg)		
	3rd	50th	97th	3rd	50th	97th	3rd	50th	97th	3rd	50th	97th
9.1	121.5	133.0	144.5	21.3	28.5	40.4	121.6	133.0	144.4	21.8	28.3	39.0
9.2	121.9	133.5	145.1	21.5	28.8	40.9	122.0	133.4	144.9	21.9	28.6	39.4
9.3	122.4	134.0	145.6	21.7	29.1	41.3	122.4	133.9	145.4	22.1	28.8	39.8
9.4	122.8	134.5	146.2	21.9	29.4	41.8	122.8	134.3	145.8	22.2	29.1	40.3
9.5	123.3	135.0	146.8	22.1	29.7	42.3	123.2	134.7	146.3	22.4	29.3	40.7
9.6	123.8	135.5	147.3	22.3	30.0	42.7	123.5	135.2	146.8	22.6	29.6	41.1
9.7	124.2	136.1	147.9	22.6	30.3	43.2	123.9	135.6	147.3	22.7	29.8	41.6
9.8	124.7	136.6	148.4	22.8	30.6	43.7	124.3	136.1	147.8	22.9	30.1	42.0
9.9	125.2	137.1	149.0	23.0	30.9	44.2	124.7	136.5	148.3	23.1	30.4	42.5
9.10	125.7	137.6	149.5	23.2	31.2	44.7	125.0	136.9	148.8	23.2	30.6	43.0
9.11	126.1	138.1	150.1	23.4	31.5	45.2	125.4	137.3	149.3	23.4	30.9	43.5
10.0	126.6	138.6	150.7	23.7	31.9	45.7	125.8	137.8	149.8	23.6	31.2	43.9

Source: WHO (available at <http://www.who.int/childgrowth/standards/en/>).

Table A-IV.3: Head circumference percentiles for girls and boys aged 0–60 months						
Month	Girls			Boys		
	3rd percentile	50th centile	97th centile	3rd percentile	50th centile	97th centile
0	31.7	33.9	36.1	32.1	34.5	36.9
1	34.3	36.5	38.8	35.1	37.3	39.5
2	36.0	38.3	40.5	36.9	39.1	41.3
3	37.2	39.5	41.9	38.3	40.5	42.7
4	38.2	40.6	43.0	39.4	41.6	43.9
5	39.0	41.5	43.9	40.3	42.6	44.8
6	39.7	42.2	44.6	41.0	43.3	45.6
7	40.4	42.8	45.3	41.7	44.0	46.3
8	40.9	43.4	45.9	42.2	44.5	46.9
9	41.3	43.8	46.3	42.6	45.0	47.4
10	41.7	44.2	46.8	43.0	45.4	47.8
11	42.0	44.6	47.1	43.4	45.8	48.2
12	42.3	44.9	47.5	43.6	46.1	48.5
13	42.6	45.2	47.7	43.9	46.3	48.8
14	42.9	45.4	48.0	44.1	46.6	49.0
15	43.1	45.7	48.2	44.3	46.8	49.3
16	43.3	45.9	48.5	44.5	47.0	49.5
17	43.5	46.1	48.7	44.7	47.2	49.7
18	43.6	46.2	48.8	44.9	47.4	49.9
19	43.8	46.4	49.0	45.0	47.5	50.0
20	44.0	46.6	49.2	45.2	47.7	50.2
21	44.1	46.7	49.4	45.3	47.8	50.4
22	44.3	46.9	49.5	45.4	48.0	50.5
23	44.4	47.0	49.7	45.6	48.1	50.7
24	44.6	47.2	49.8	45.7	48.3	50.8
25	44.7	47.3	49.9	45.8	48.4	50.9
26	44.8	47.5	50.1	45.9	48.5	51.1

Month	Girls			Boys		
	3rd percentile	50th centile	97th centile	3rd percentile	50th centile	97th centile
27	44.9	47.6	50.2	46.0	48.6	51.2
28	45.1	47.7	50.3	46.1	48.7	51.3
29	45.2	47.8	50.5	46.2	48.8	51.4
30	45.3	47.9	50.6	46.3	48.9	51.5
31	45.4	48.0	50.7	46.4	49.0	51.6
32	45.5	48.1	50.8	46.5	49.1	51.7
33	45.6	48.2	50.9	46.6	49.2	51.8
34	45.7	48.3	51.0	46.6	49.3	51.9
35	45.8	48.4	51.1	46.7	49.4	52.0
36	45.9	48.5	51.2	46.8	49.5	52.1
37	45.9	48.6	51.3	46.9	49.5	52.2
38	46.0	48.7	51.3	46.9	49.6	52.3
39	46.1	48.7	51.4	47.0	49.7	52.4
40	46.2	48.8	51.5	47.0	49.7	52.4
41	46.2	48.9	51.6	47.1	49.8	52.5
42	46.3	49.0	51.6	47.2	49.9	52.6
43	46.4	49.0	51.7	47.2	49.9	52.7
44	46.4	49.1	51.8	47.3	50.0	52.7
45	46.5	49.2	51.8	47.3	50.1	52.8
46	46.5	49.2	51.9	47.4	50.1	52.8
47	46.6	49.3	51.9	47.4	50.2	53.0
48	46.7	49.3	52.0	47.5	50.2	53.0
49	46.7	49.4	52.1	47.5	50.3	53.0
50	46.8	49.4	52.1	47.5	50.3	53.1
51	46.8	49.5	52.2	47.6	50.4	53.1
52	46.9	49.5	52.2	47.6	50.4	53.2
53	46.9	49.6	52.3	47.7	50.4	53.2
54	47.0	49.6	52.3	47.7	50.5	53.3
55	47.0	49.7	52.4	47.7	50.5	53.3
56	47.1	49.7	52.4	47.8	50.6	53.4
57	47.1	49.8	52.5	47.8	50.6	53.4
58	47.2	49.8	52.5	47.9	50.7	53.5
59	47.2	49.9	52.6	47.9	50.7	53.5
60	47.2	49.9	52.6	47.9	50.7	53.5

Courtesy: World Health Organization. Available at: <http://www.who.int/childgrowth/standards/en/>. Accessed on: 29 June 2011.

APPENDIX M HIPPOCRATIC OATH

(To be administered at the time of admission to the medical profession)

- I solemnly pledge/to consecrate my life/to the service of humanity.
- I will give to my teachers/the respect and gratitude/which is their due.
- I will practice my profession/with conscience and dignity.
- The health of my patients will be/my first consideration.
- I will respect the secrets/which are confided in me.
- I will maintain by all means in my power/the honor and the noble tradition of the medical profession.
- My colleagues will be my brothers.
- I will not permit consideration of religion, nationality, race, party politics or social standing/to intervene between my duty and my patients.
- I will maintain the utmost respect for human life/from the time of conception.
- Even under threat, I will not use my medical knowledge. Contrary to the law of humanity.
- I make these promises/solemnly, freely and upon honor.

Weight-for-age GIRLS

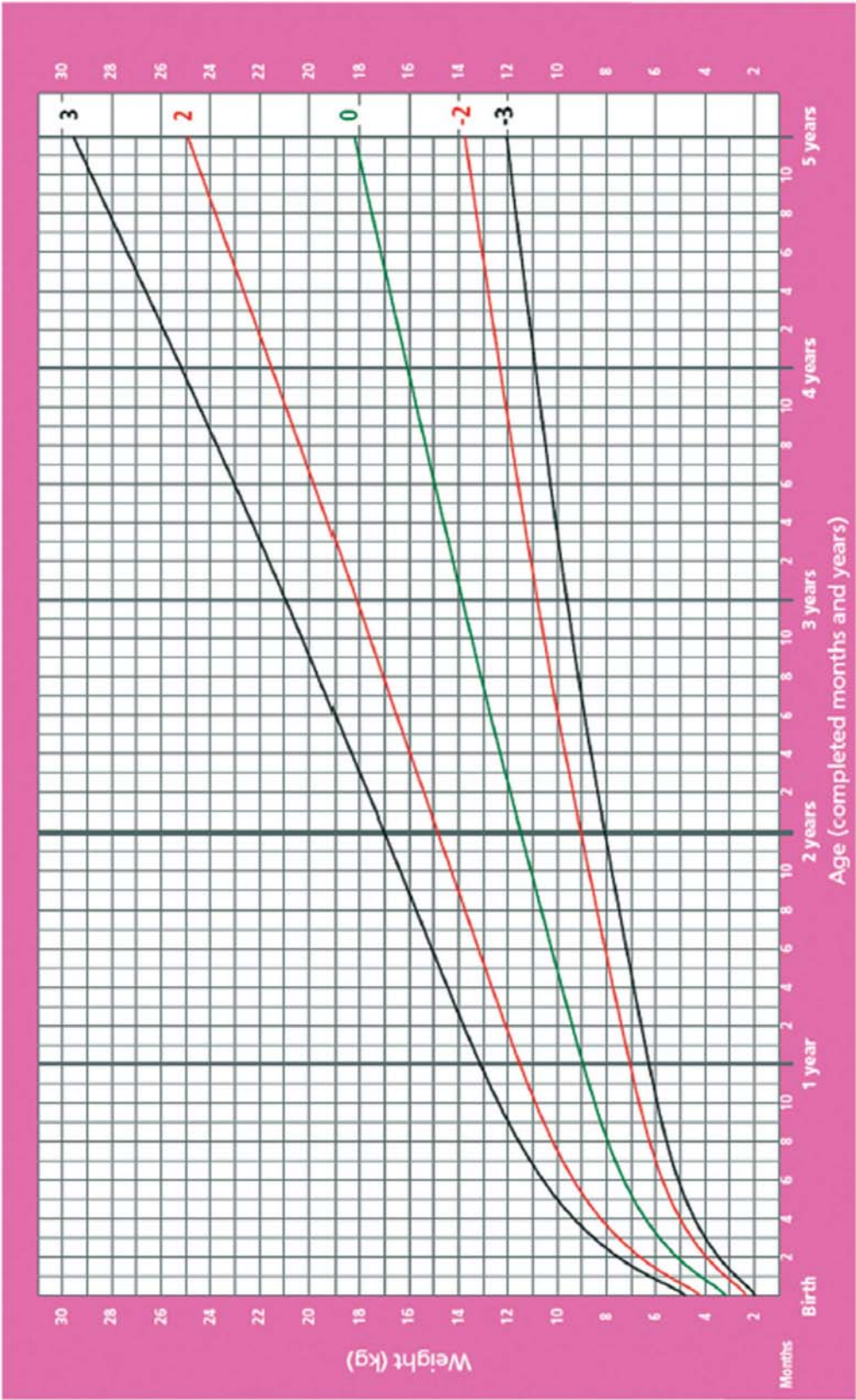
Birth to 5 years (percentiles)



WHO Child Growth Standards

Weight-for-age GIRLS

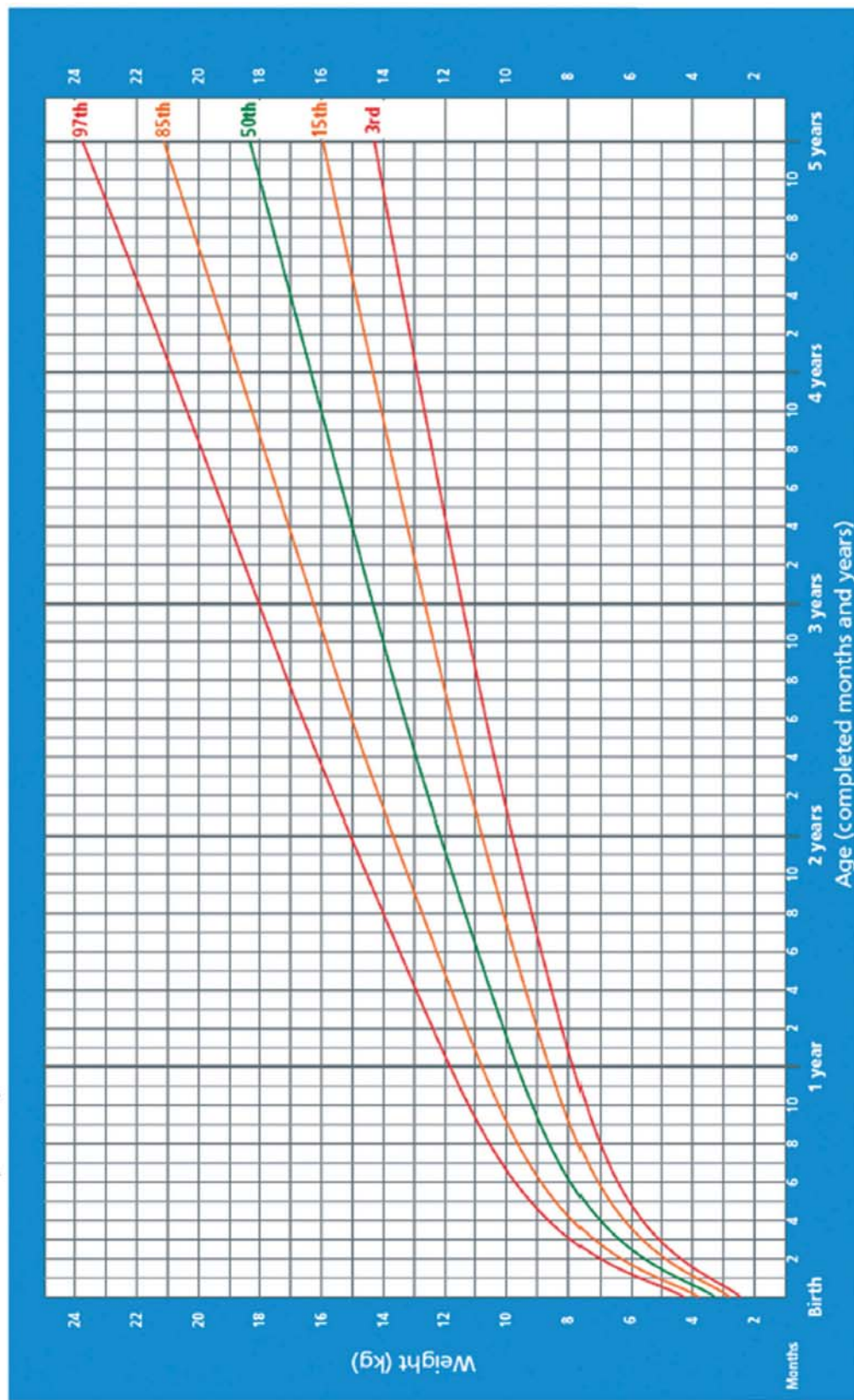
Birth to 5 years (z-scores)



WHO Child Growth Standards

Weight-for-age BOYS

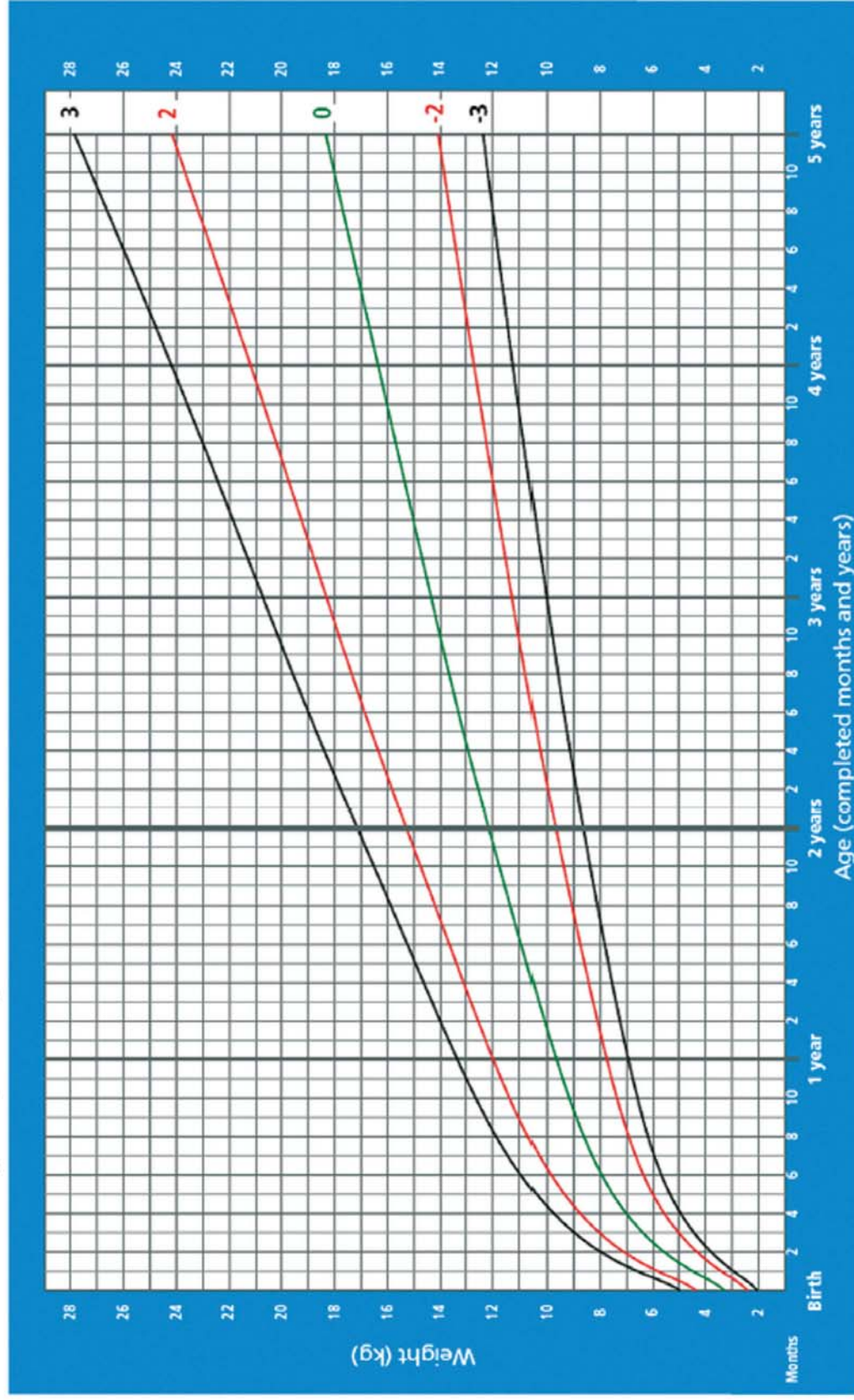
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WHO Child Growth Standards

Weight-for-age BOYS

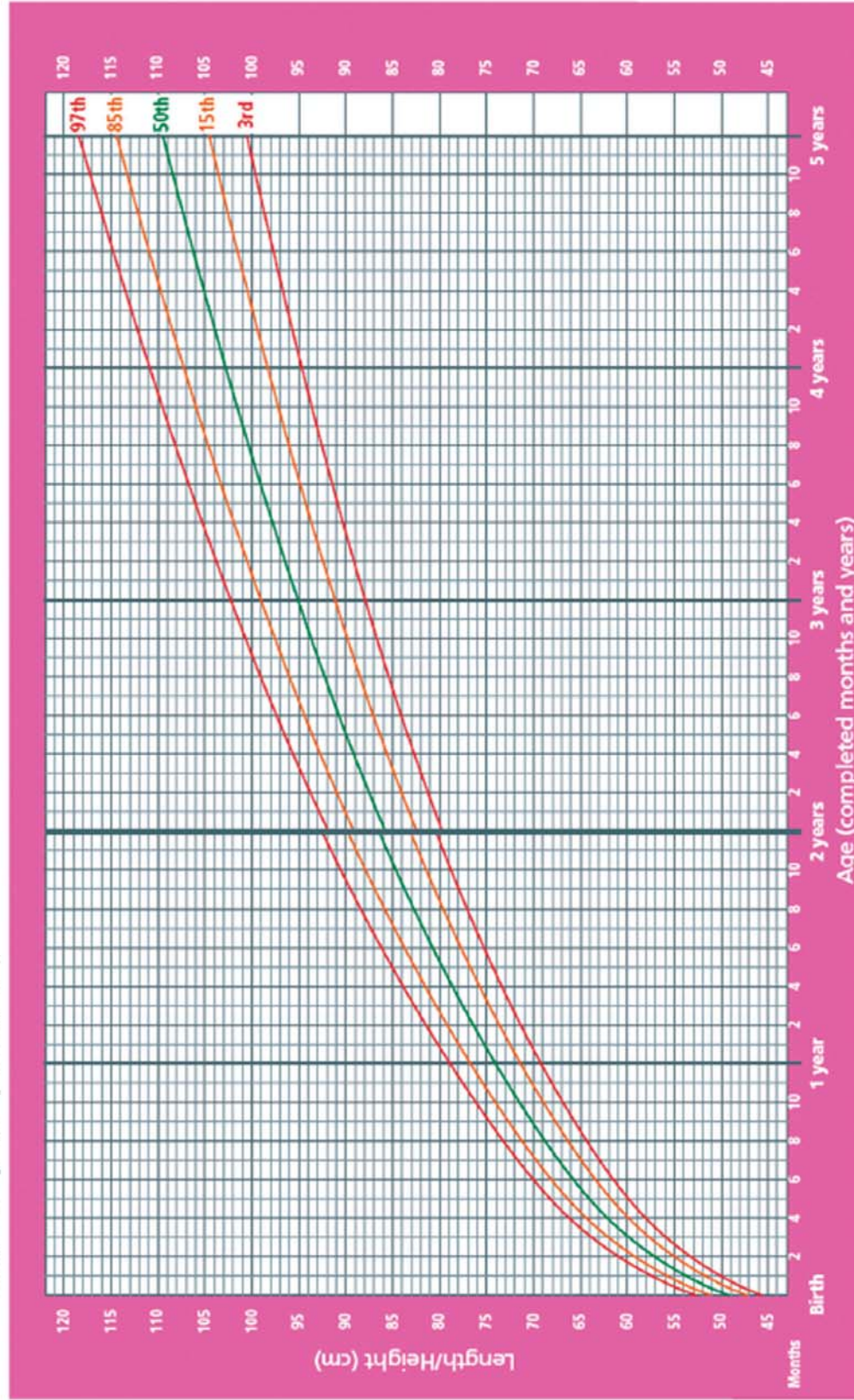
Birth to 5 years (z-scores)



WHO Child Growth Standards

Length/height-for-age GIRLS

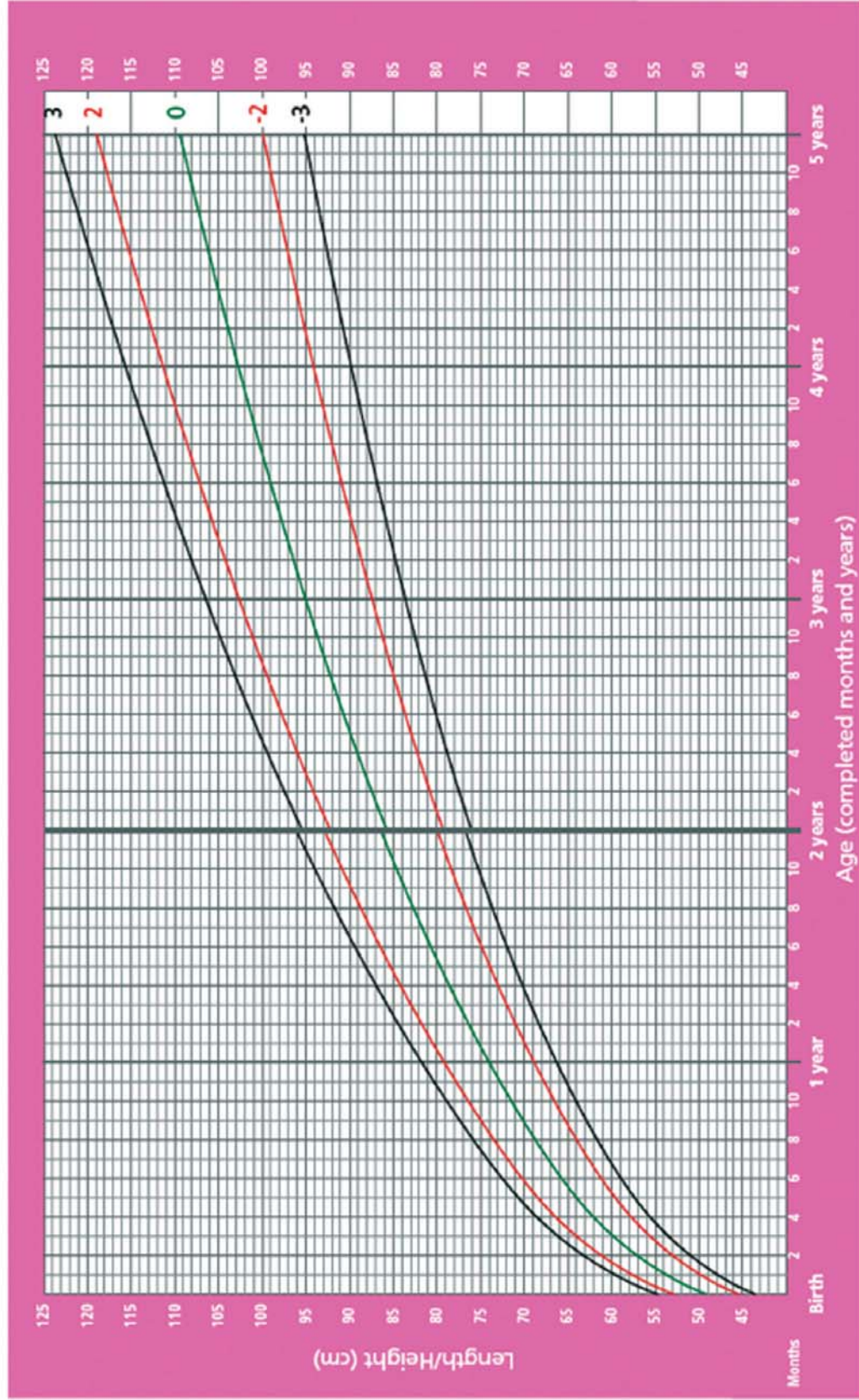
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WHO Child Growth Standards

Length/height-for-age GIRLS

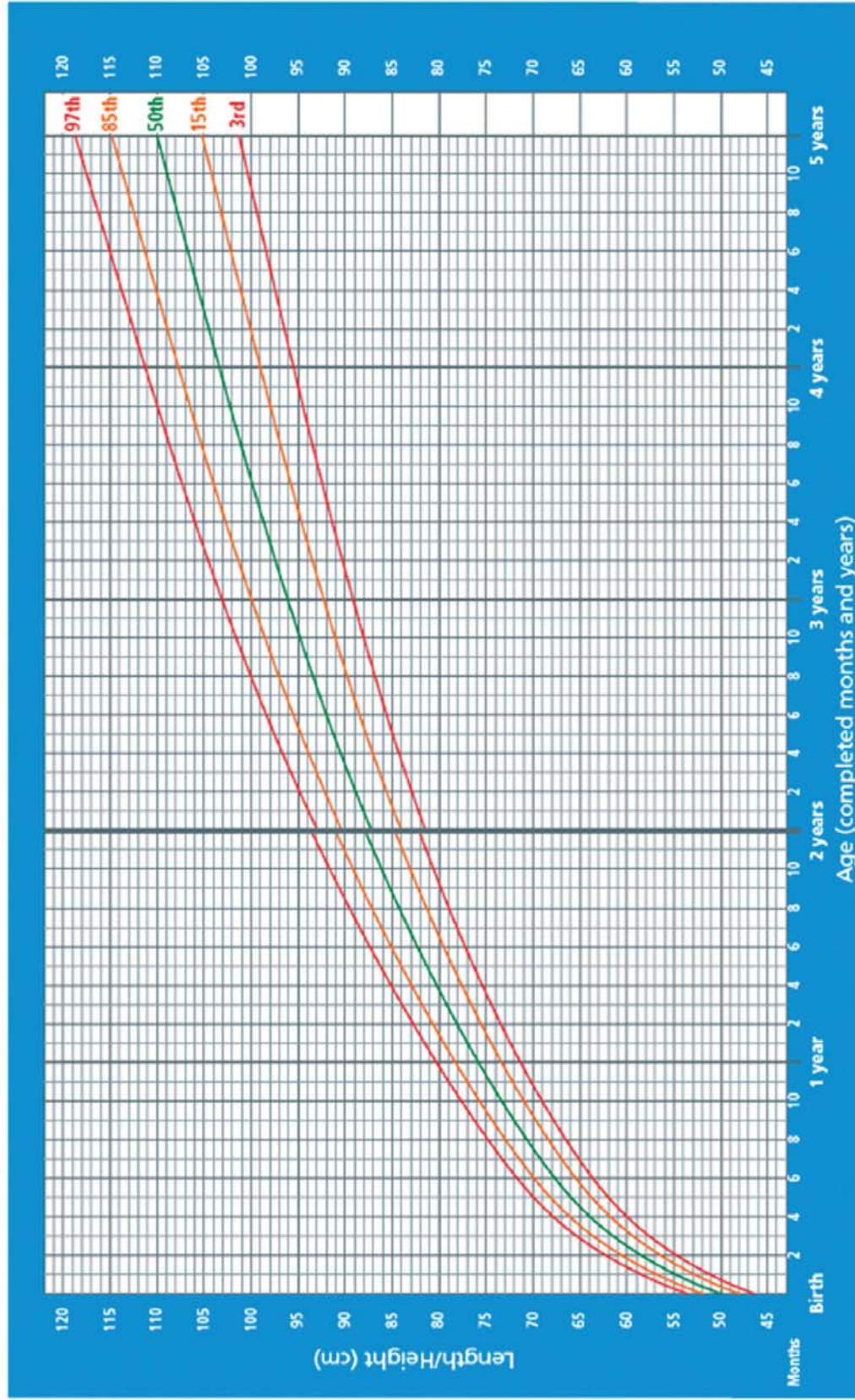
Birth to 5 years (z-scores)



WHO Child Growth Standards

Length/height-for-age BOYS

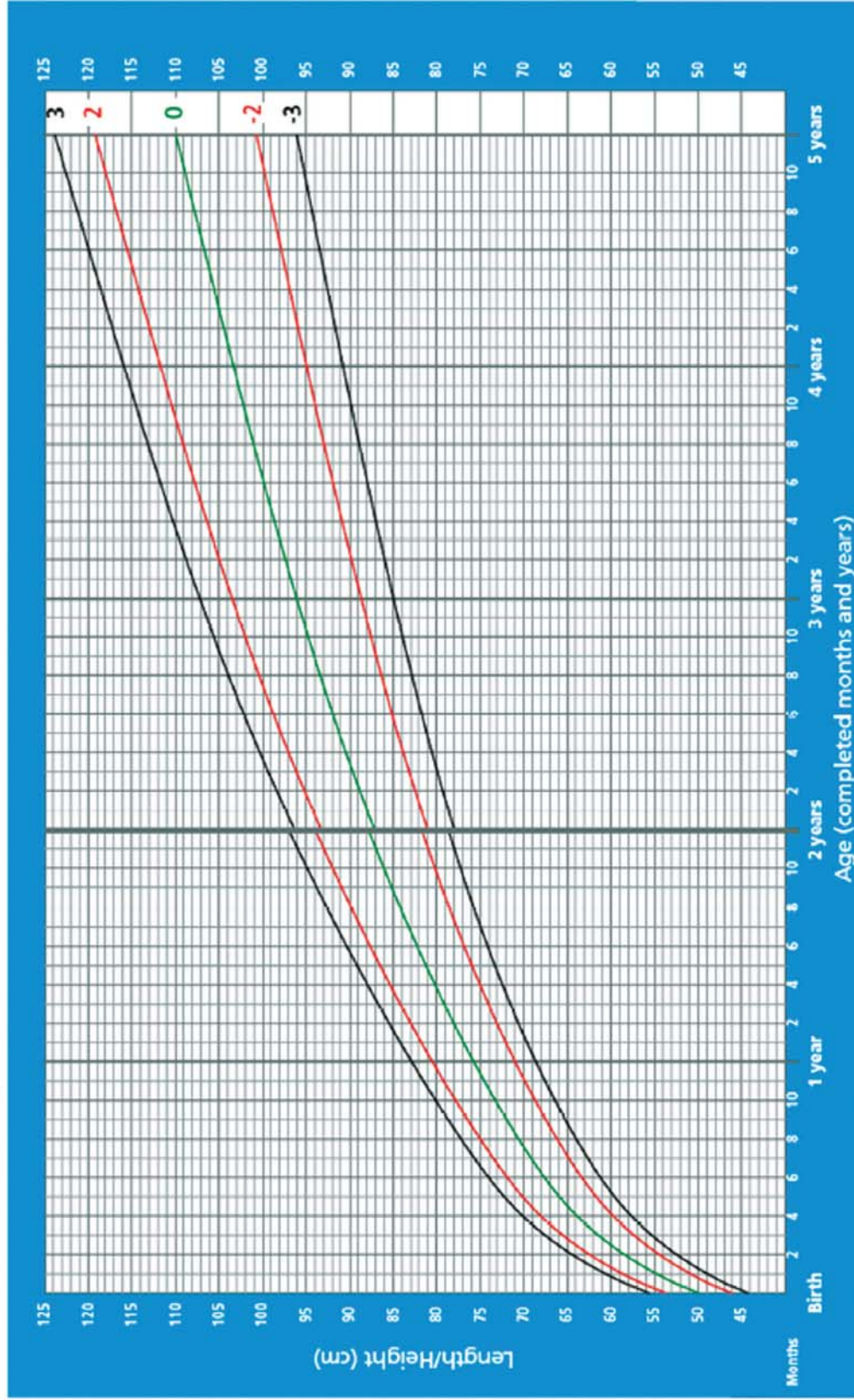
Birth to 5 years (percentiles)



WHO Child Growth Standards

Length/height-for-age BOYS

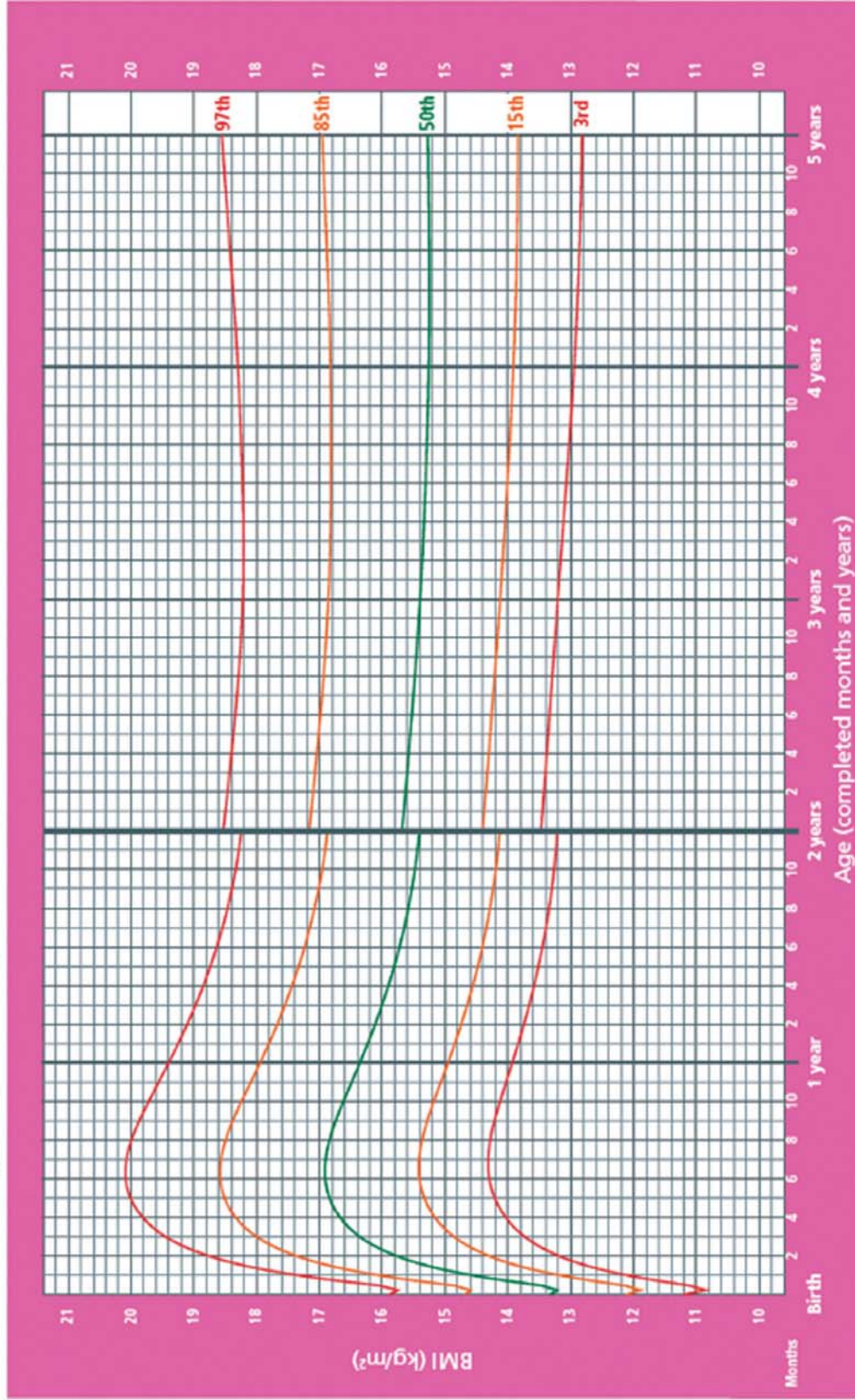
Birth to 5 years (z-scores)



WHO Child Growth Standards

BMI-for-age GIRLS

Birth to 5 years (percentiles)



WHO Child Growth Standards

BMI-for-age GIRLS

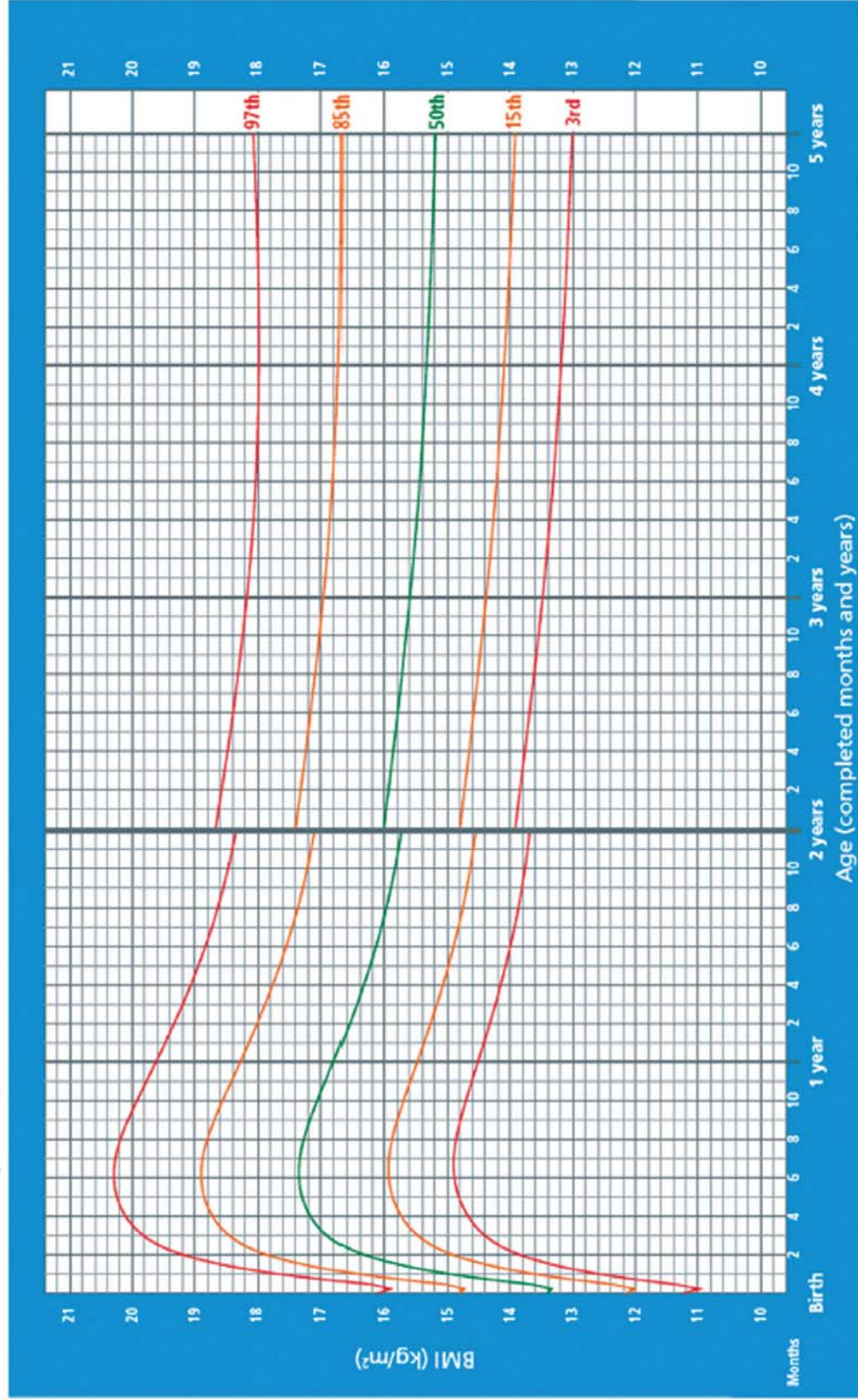
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WHO Child Growth Standards

BMI-for-age BOYS

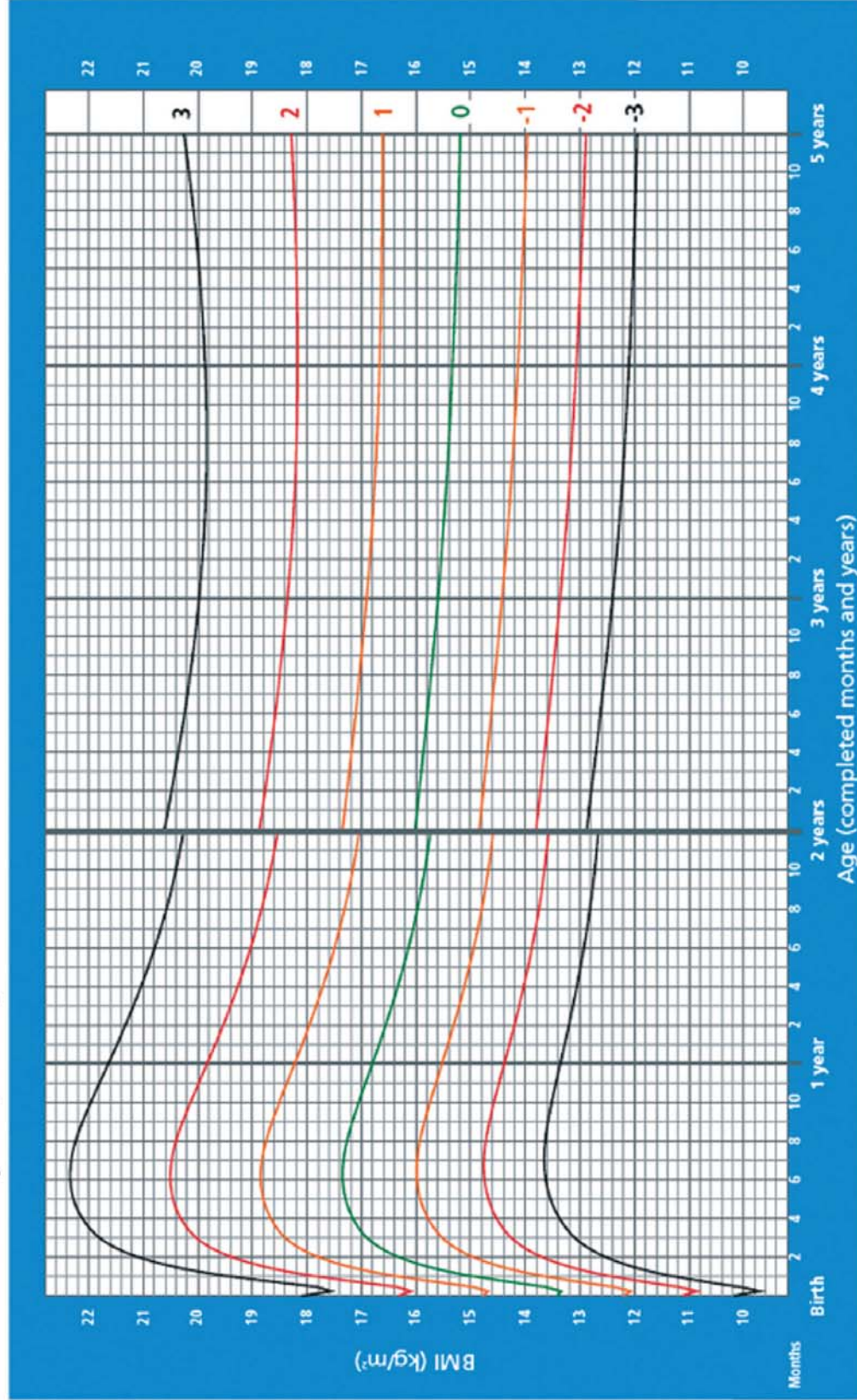
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Birth to 5 years (z-scores)



WHO Child Growth Standards

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